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Complications of Heart Valve Replacement

Embolism, Bleeding and Hemolysis

MALCOLM M. MC HENRY, M.D., EDWARD A. SMELOFF, M.D., AND
PAUL G. HATTERSLEY, M.D., *Sacramento*

■ *Fifty-two patients surviving single heart valve replacement since September 1962 were reviewed in order to detail the incidence of post-operative embolism, bleeding and hemolysis. A substantial decrease in the occurrence of embolism has been seen with newer prosthetic devices paralleling the improvement in cardiac catheterization dynamics. The frequency of embolism appears also to be affected by the degree and adequacy of anticoagulant control although a higher morbidity from bleeding must be accepted. The tendency to deformation and destruction of red cells by rigid prosthetic valves is apparent since shortened red cell survival indicative of hemolysis was found in all patients studied. Hemolytic anemia of importance was uncommon.*

SURGICAL REPLACEMENT of the aortic, mitral and tricuspid valves has been responsible for substantial clinical and hemodynamic improvement in patients with valvular heart disease. Unfortunately the insertion of prosthetic valves into the vascular system of man has entailed complications. In a significant number of patients heart disease has been palliated at the risk of systemic embolism, bleeding and hemolytic anemia. The true incidence of these complications is unknown. This report summarizes our experience with these conditions in 52 patients who have survived single valve re-

placement from September 1962 to October 1967 and who have been evaluated for three to 64 months after operation.

Nature of the Prosthetic Device

The prosthetic valve used in the early operations in the series (Figure 1) consisted of an open-ended four-strut cage with a flat annulus in which a silastic ball seated at approximately 85 percent of the orifice diameter.¹ The open cage design was chosen to decrease clot formation at the apex of the cage. This device, called the Cartwright-Palich valve, was in clinical use from September 1962 to August 1963.

After extensive engineering studies at Sacramento State College, this valve was redesigned so that ball closure occurred within the confines of a

From the Departments of Medicine, Surgery and Pathology, and the Cardiopulmonary Laboratory, Sutter Memorial Hospital, Sacramento.

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Reprint requests to: Cardiopulmonary Laboratory, Sutter Memorial Hospital, 52nd and F Streets, Sacramento 95819 (Dr. McHenry).

smaller upstream cage.² Consequently the ball seated at 100 percent of its diameter. This was advantageous in that it permitted a larger orifice area without an increase in the size of the ball. Also, mechanical obstruction was reduced. Preliminary studies with the Starr-Edwards caged ball valve had indicated that obstructive gradients were inherent in orifice-seating valves.³

The newer prosthetic valve was extensively tested in a pulse duplicator system and ideal cage length to permit highest flow with minimal obstructive gradients was determined. The valve annulus remained flat as in the previous design. This valve, called the SCDK (Figure 1), was used from September 1963 to September 1964.

The latest modification is known as the Smeloff-Cutter valve* (Figure 1). In it the annulus has been rounded and sharp edges perpendicular to flow have been eliminated to reduce the tendency to stasis and clot formation. A larger Teflon sewing ring has been added. Mitral and aortic valves differ only in the size of this ring. Since previous catheterization studies had suggested that silastic balls may swell and contribute to obstructive gradients,⁴ balls are now pre-swollen by heating at body temperature. Clearance between the ball and the throat of the orifice remains at .003 to .005 inches.

*Cutter Laboratories, Berkeley, California.

Results

Embolism

Systemic embolism was identified objectively when sudden vascular occlusion occurred in patients without obvious preexisting coronary, cerebrovascular or peripheral vascular disease. Transient findings of vascular obstruction in this series of patients were assumed to be embolic in origin.

Seven patients (14.6 percent) had had systemic embolism before operation. In one patient with Ebstein's anomaly,⁵ paradoxical embolism across an atrial septal defect occurred on three occasions, presumably due to active iliofemoral thrombophlebitis. In five patients undergoing mitral valve replacement, atrial clots were discovered and removed. Two of these subjects were found to have cerebral emboli immediately after operation.

Clinical evidence of systemic embolism was noted postoperatively in eight patients with an equal incidence in aortic and mitral valve replacements (Table 1). Although the majority of clots were evident within the first 15 months, in two patients emboli developed for the first time 22 and 38 months after operation. In the latter patient severe mitral valve obstruction occurred 52 months after surgical replacement with a Cartwright-Palich mitral valve, and he was found at repeat operation to have clotting within the prosthetic valve.

TABLE 1.—Patients with Postoperative Emboli*

Patient	Age	Type Surgery	Valve Type	Valve Area (CM ²)	Rhythm	Time of Embolism	Anticoagulants	Comments
1	44	Mitral	C-P	2.54	AF	1 year	intermittent and poorly controlled	clotted valve; died 1 year after implant
2	40	Mitral	C-P	3.88	AF	38 mos. 52 mos.	well controlled	2 cerebral emboli; valve found clotted at repeat surgery 53 mo. later
3	36	Aortic	C-P	2.1	SR	15 mos.	intermittent and poorly controlled	emboli to brain and lower extremities; valve replaced with SCDK because of AI and emboli
4	48	Mitral	C-P	3.5	AF	14 mos.	well controlled	hemiplegia
5	47	Aortic	SCDK	2.85	SR	4 mos.	well controlled	saddle embolism, luetic AI
6	44	Mitral	SCDK	4.1	AF	22 mos.	well controlled	cerebral, abdominal and extremity emboli; LV failure at heart catheterization; no MI
7	55	Aortic	SCDK	2.85	SR	7 mos.	none	cerebral embolism; bled postoperatively on anticoagulants; restarted after embolism
8	8	Aortic	SCDK	2.31	SR	6 mos.	none	embolism to leg; surgery November 1964

LEGEND

- C-P Cartwright-Palich valve
- SCDK Smeloff-Cartwright-Davey-Kaufman valve
- AF Atrial fibrillation
- SR Sinus rhythm
- AI Aortic insufficiency
- MI Mitral insufficiency

*Listed in order of operation

A high frequency of embolism was noted in patients with earlier prototype valves: It occurred in four of seven patients with a Cartwright-Palich valve and in four of 15 patients with SCDK valves. Since May 1965, no apparent emboli have been identified in 30 patients surviving replacement with a Smeloff-Cutter valve in follow-up for periods of from three to 33 months. The overall incidence of embolism since 1962 was 15.4 percent.

Early in our experience, anticoagulation was not pursued in all patients, especially if there was a history of previous bleeding or there were post-operative hemorrhagic complications or the patient was unreliable or a child.⁶ Of patients with post-operative embolism four (three aortic and one mitral) either took no anticoagulants or anticoagulant control was poorly maintained. One of these died of a clotted valve. Adequate therapy was prescribed and monitored for the other three and they had no recurrence. Poor anticoagulant control appeared to contribute significantly to embolism in half of the patients. In the entire series, ten patients were denied anticoagulants or were poorly controlled as outpatients. Embolism developed in four of them.

Two patients had transient embolic symptoms after undergoing diagnostic heart catheterization. Anticoagulant therapy was discontinued in both of them to permit postoperative study of prosthetic mitral valve function. The findings cleared and there have been no residua.

Bleeding

In an attempt to suppress thrombus formation,

Warfarin sodium was given in doses sufficient to increase prothrombin-proconvertin times to two and a half times normal. In patients with previous history of bleeding, anticoagulation was pursued cautiously, with doses adequate to increase the clotting time to one and a half times normal. In the latter group determinations were obtained at seven- to fourteen-day intervals.

Bleeding important enough to require admittance to hospital, transfusion or cessation of anticoagulants occurred in seven patients (13.6 percent), none of whom had bled before. In three of them, bleeding occurred from the gastrointestinal tract. Episodes were mild in two and nearly fatal in the other. Two patients had hemothorax post-operatively after anticoagulants were begun. One patient died of massive cerebral hemorrhage three months after successful aortic valve replacement. The last patient experienced pronounced hematuria and bleeding about the face. Five of these patients with severe bleeding were found at the time of admittance to hospital to have prothrombin time three to five times normal.

The exact incidence of minor bleeding in this series is unknown. Numerous hematomas and instances of transient hematuria and hemoptysis were recorded. There were also isolated instances of epistaxis. Usually all that was needed was minor adjustment in drug dosage.

Hematologic Findings

We performed comprehensive hematologic evaluation of 17 patients at intervals of seven to thirty-five months after operation. Studies included de-

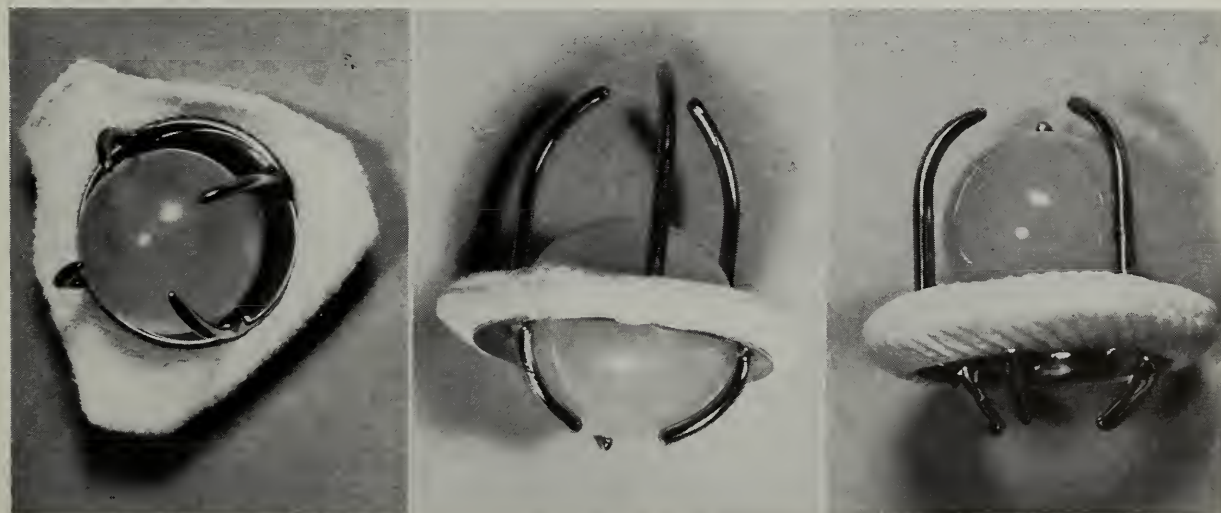


Figure 1.—*Left*, Cartwright-Palich valve used in replacement operations from September 1962 to August 1963. *Center*, SCDK valve used from September 1963 to September 1964. *Right*, latest modification, the Smeloff-Cutter valve which has been used since mid-1964.

TABLE 2.—Hematologic Results
Mitral valve replacements

Patient	HGB	RBC mass	RBC 50% survival (days)	LDH	Serum Fe	% saturation	Plasma iron turnover (mg/Kg/day)	RBC iron turnover (mg/Kg/day)	% RBC iron utilization	Serum haptoglobin	Comments
1*	11.9	23.5	24	480	25	9.8	0.22	0.19	84.5	7.0	decreased iron turnover; Fe deficiency; moderate mitral regurgitation
2*	11.2	18.9	23	750	95	27.0	0.59	0.46	78.0	19.0	decreased RBC mass; moderate mitral regurgitation; mild hemolysis
3	12.4	27.4	30	412	60	21.0	0.61	0.55	89.1	13.3	minor hemolysis
4	15.0	31.4	22.5	832	219	64.0	1.07	0.88	82.0	79.5	mild hemolysis; LV failure
5	15.0	25.4	18.5	1310	150	47.0	1.21	0.94	77.4	—	decreased RBC mass; mild mitral regurgitation
6*	10.4	19.0	24.0	602	85	32.0	0.50	0.40	78.1	14.0	LV failure without mitral regurgitation
7	16.1	28.1	24.0	908	85	20.6	0.72	0.61	84.2	—	plasma hemoglobin 18 per 100 ml; mild hemolytic anemia; no MI
8*	11.0	19.8	23.0	502	85	31.0	0.56	0.49	86.5	13.7	borderline Fe deficiency
9	15.5	25.6	24.0	514	150	50.0	0.75	0.63	84.0	12.8	low RBC mass; Fe deficient; decreased Fe turnover
10	12.8	26.4	30.0	564	70	15.0	0.52	—	—	9.0	decreased Fe turnover
11*	11.5	21.9	24.5	1072	55	14.7	0.30	0.25	82.6	27.6	mild hemolysis; mild AI; poor Fe utilization
12	13.6	27.0	23.0	438	55	21.5	0.35	0.28	78.0	9.4	minor hemolysis
13	13.0	25.7	15.0	542	185	54.0	0.80	0.31	38.4	—	gross AI from detached prosthesis; moderate hemolytic anemia; decreased RBC mass; Fe deficiency; plasma Hgb 35 mg. %
14*	11.5	23.2	23.0	340	75	25.0	0.63	0.56	88.0	24.0	mild hemolytic anemia; moderate AI subsequent to valve replacement
15	10.5	20.9	16.5	1240	35	8.1	0.69	0.63	91.4	—	moderate AI; compensated hemolytic anemia; plasma Hgb 18 mg per 100 ml
16*	14.6	31.5	15.0	1370	160	44.0	2.0	1.6	78.3	10.5	7 mo. after initial study
	12.3	23.9	15.0	2000	90	21.0	1.3	1.0	76.5	—	
17	12.5	—	16.0	3208	115	31.0	0.52	—	—	7.4	
	14.2	26.2	24.0	848	—	—	—	0.47	91.4	9.7	

NORMAL VALUES

RBC mass	25-35 cc/Kg
RBC survival	25-35 days
LDH	up to 350 units
Fe	60-150 Mg. %
% Fe saturation	over 15 %
Plasma iron turnover	0.46-0.78 mg/Kg/day
RBC iron turnover	0.32-0.72 mg/Kg/day
Iron utilization by RBC's	75-100 %
Haptoglobin	45-127 mg. %

LEGEND

HGB	Hemoglobin
RBC	Red blood cell
IDH	Lactic acid dehydrogenase
Fe	Iron
LV	Left ventricle
AI	Aortic insufficiency
MI	Mitral insufficiency

* Anemic patients

termination of hemoglobin and red cell mass by the radioactive chromium technique, as evaluation of the degree of anemia; red cell survival studies with radioactive chromium,^{7,8} as a determinant of the rate of hemolysis or blood loss; direct anti-globulin (Coombs), total lactic acid dehydrogenase (LDH) and isoenzymes,⁹ and serum haptoglobin,^{10,11} as further evidence of abnormal hemolysis; and serum iron and iron-binding capacity and ferrokinetics with radioactive iron,¹² as evidences of rate of hemoglobin production. Table 2 lists the findings.

We encountered substantial increases in LDH and fraction 1 isoenzymes in all patients, and all but one patient showed depressed haptoglobin. Such changes occur regularly with intravascular hemolysis.¹³ All direct anti-globulin tests, on the other hand, proved negative.

Eight of the 17 patients showed some degree of anemia at the time of the radioisotope studies (hemoglobin 10.4 to 12.3 gms per 100 ml; red cell mass 18.9 to 23.9 ml per kg of bodyweight). Others were anemic at other times. All of those with anemia showed decidedly shortened to borderline low erythrocyte survival (50 percent survival: 15.0 to 24.5 days). With a single exception, none showed the increase in effective erythropoiesis which normally results from increased hemolysis. The erythrocyte iron utilization was normal (0.32 to 0.72 mg per kg per day) in five and decreased in two (Cases 1 and 11). The single exception (Case 16) with only borderline anemia and much shortened erythrocyte survival (15.0 days half life) showed an increase in erythrocyte iron utilization (1.0 mg per kg per day) which was inadequate to produce an entirely normal picture.

In one patient (No. 15) it was demonstrated that a much shortened red cell survival alone would not produce anemia, providing the bone marrow compensates adequately. With a 50 percent survival time of only 16.5 days and normal red cell production apparently depressed due to iron deficiency (RBC iron turnover 0.63 mg per kg per day), he was definitely anemic. When he was treated with iron, the erythrocyte iron turnover increased materially and while the rate of red cell destruction did not improve, the hemoglobin level and red cell mass returned to normal. One other patient (No. 11) showed borderline iron deficiency and decreased erythrocyte production.

Although the shortest red cell survival times were found in patients with angiographically detectable aortic insufficiency, three patients with mitral insufficiency had normal survival times and two patients without mitral prosthetic reflux had compensated hemolysis. Therefore red cell trauma associated with valvular incompetence did not appear to be the sole reason for hemolysis.

Discussion

Complications of various kinds have followed successful heart valve replacements with caged-ball prosthetic valves. These include systemic embolism,^{14,20} major intra-vascular hemolysis,^{17,21-26} jaundice without hepatitis,²⁷ deterioration in renal function,²⁸ psychiatric changes,²⁹ and disruption or variance of silastic ball occluders.^{30,31} A low mortality and low frequency of such complications would be tolerable because of the poor prognosis of patients without surgical replacement. Yet the frequency of these complications—specifically systemic embolism—has led to continued disability in survivors and has influenced some surgeons to attempt palliative repair of diseased valves rather than replacement.

Certain parallels exist to explain embolism in the patient who does not have operation and in the subject with valve replacement. Measurable abnormalities in cardiac function correlate well with intracardiac thrombosis and systemic embolism in patients with rheumatic mitral valve disease.³²⁻³⁴ Operative treatment of mitral stenosis, without prosthesis, has been observed to have substantially reduced the recurrence rate of embolism coincident with improvement in hemodynamic function.³⁵⁻³⁷ If valve replacement is performed in such cases, the incidence of embolism may be expected to exceed the preoperative incidence.

Postoperative catheterization studies show that caged-ball prosthetic valves are inherently obstructive.³ Transvalvular pressure gradients persist at rest and during exercise. The cardiac output with effort may be impaired.³⁸⁻⁴⁰ These changes may influence clot formation. Important hemodynamic impairment was noted in three patients in the present series in whom emboli developed postoperatively (Table 1). In one of them, leaking of a prosthetic aortic valve caused ventricular failure. In the others there were increases in left ventricular filling pressure and volume and decrease in cardiac output without evidence of regurgitation about the prosthetic mitral valve.

TABLE 3.—*Patients with Smeloff-Cutter Valves Restudied* by Heart Catheterization*

Patient	Sex	Age	Type Valve	Months Implanted	Valve Gradient (mm Hg)	Resting CI	LA Pressure	LV Pressure	Comments
1	F	36	Aortic	25	12	3.6	8	130/9	
2	M	63	Mitral	24	4	1.9	11	132/7	Myocardial infarction; valve replaced because of papillary muscle rupture
3	F	43	Aortic	22	20	3.5	12	193/11	
4	M	37	Aortic	20	21	2.8	12	123/10	Moderate residual AI; mild hemolytic anemia; working
5	M	44	Mitral	14	5	2.5	18	121/11	Died of fulminant acute myocarditis; had been working
6	F	54	Aortic	18	10	2.8	8	172/10	
Pre-swollen Ball									
7	M	45	Mitral	12	2	2.9	13	120/10	Working
8	F	58	Mitral	10	3	2.8	12	154/11	Mild hemolysis without anemia; Positive Coombs test
9	M	49	Aortic	8	10	3.1	11	154/9	Working
10	F	57	Mitral	6	2	2.4	10	140/10	Residual tricuspid stenosis and insufficiency
11	F	58	Aortic	11	13	3.1	10	145/8	Working; minor AI

LEGEND

CI Cardiac index
 LA Left atrium
 LV Left ventricle
 AI Aortic insufficiency

*Period of follow-up to January 1968

NORMAL VALUES

Cardiac index 2.7 L/M²
 Left atrium 13 mm Hg or less
 Left ventricle diastolic less than 14 mm Hg

The incidence of postoperative emboli has decreased significantly with time, in part due to changes in engineering design of valves and to the subsequent normalization of hemodynamic function. Using the earlier SCDK valve, Cooley and coworkers⁴⁰ reported a 4 percent incidence of embolism in 250 patients followed for from three to twelve months. Shortening of the cage and the use of cloth to cover a redesigned annulus has lowered the incidence of embolism following Starr-Edwards mitral valve replacements from 38 percent to 3 percent since March 1965.⁴² Yeh and coworkers⁴³ detected no emboli in 36 patients with Starr-Edwards aortic valve replacements.

No emboli were noted in 30 patients with Smeloff-Cutter mitral or aortic valves followed for from three to thirty-three months. Design changes may have played an important role in suppressing them. In a previous report of 15 patients, normal function was demonstrated in all but one after aortic valve replacement; but significant pressure gradients, elevation of left atrial pressure, low cardiac output and inappropriate output responses to exercise were reported in eight patients with mitral replacements.⁴ To a certain extent swelling of the silastic ball due to absorption of blood

lipid elements may have been responsible. Nine of the 15 patients studied had either Cartwright-Palich or SCDK prosthetic valves. Six had Smeloff-Cutter valves without pre-swollen balls. Five patients (three with mitral valves) were restudied after replacement with the latest valve design including the pre-swollen ball (Table 3). Low resting pressures and gradients were found in all of them and cardiac function was substantially improved over preoperative function. Pre-swelling of the silastic ball appears an important cause for this improvement. The high incidence of embolism with earlier prototype valves parallels the demonstrated hemodynamic abnormalities.

Systemic embolism with sole aortic valve disease has been rare but occurs with frequency after prosthetic replacement. This finding suggests that the foreign material is itself thrombogenic. Davila and coworkers⁴⁴ stressed that clotting will occur when an exposed interface exists between the endothelium and the prosthetic material. However, in calves with mitral replacements using a Dacron felt ring and a polypropylene occluder,⁴⁵ and in tricuspid replacements using a totally cloth-covered caged ball valve,⁴⁶ thrombi have been eliminated.

Anticoagulant therapy may substantially alter this thrombogenic tendency. After earlier indecision about its effectiveness⁴⁷ prevention of embolism has been noted by Yeh and coworkers⁴³ and by Duvoisin and his associates⁴⁸ in patients under close and adequate control with Warfarin sodium. In both series it was apparent that inadequate therapy increased the risk of embolism but that the protection afforded by suboptimal dosage was superior to no drug therapy at all. A reduction in the incidence of embolism from 44 percent to 5 percent with the use of Warfarin sodium was demonstrated in a review of 111 patients reported by Gadboys and coworkers.⁴⁹ In the present series half of the patients with emboli were untreated or poorly controlled. The total incidence of embolism in such patients was 40 percent.

The success in preventing embolism has been counterbalanced by a high incidence of bleeding, and the risk of hemorrhage seems to parallel the intensity of anticoagulant therapy. Major bleeding attributable to anticoagulants was noted in seven (13.6 percent) of our 52 patients, with one death. None of the seven had a previous history of peptic ulcer or abnormal bleeding. Five of them had excessive prolongation of prothrombin-proconvertin activity. This incidence of bleeding is greater than the 8.8 percent and 8.1 percent, respectively, reported by Yeh and coworkers⁴³ and Gadboys and coworkers.⁴⁹ To avoid this complication more frequent blood checks are advised and close patient observation is necessary since in all cases bleeding of major importance was occult.

Intravascular hemolysis, often well-compensated, is a rather common complication of valve replacement. Its importance stems from the altered cardiac function produced by anemia,⁵⁰ from the potentially harmful effects of chronic hemoglobinuria on renal function⁵¹ and from the well-established thrombogenic effect of elevated plasma hemoglobin. The occurrence and severity of anemia clearly depend on the degree of shortening of red cell survival, whether shortened by abnormal hemolysis or blood loss and by the adequacy of compensatory increases in red cell production of which the bone marrow is capable. Hemolysis has been demonstrated in patients who have had severe aortic valve obstruction before operation,²³ but after operation its appearance correlates well with prosthetic valvular regurgitation. In some iron-deficient patients, iron administration has brought about compensation of the anemia⁵²

whether related to blood loss, inadequate iron intake or increased urinary iron excretion.⁵³ Such was true in Case 15. We have not seen abnormal hemolysis related to an auto-immune mechanism.

In this series all of 17 patients in whom this was studied had shortened red blood cell survival indicating hemolysis, although in only two was significant anemia found. Such hemolysis is not unexpected since trauma to red cells may be anticipated when any rigid foreign material is placed within the cardiac chambers.²³ Similar effects from trauma have been reported postoperatively in patients with atrial septal defects and mitral valvular insufficiency when the regurgitant jet strikes a Teflon prosthetic patch⁵⁴ and in patients with lucite prosthetic devices inserted to palliate aortic insufficiency.⁵⁵

A tendency to deformation and destruction of red cells was found in all patients, as evidenced by elevation of serum LDH, depression of serum haptoglobins and shortening of RBC survival. In nine patients this tendency was pronounced enough to shorten red cell survival. Anemia occurred once when mechanical fragility was potentiated by severe valvular regurgitation. Mild leakage about the prosthetic valve appears to be tolerated well without evidence of hemodynamic or hematologic deterioration.

Therefore resistance to potential hemolytic anemia occurs in spite of an almost uniform tendency to hemolysis. Apparently the marrow can adequately compensate in most cases and as long as red blood cell iron turnover and utilization are maintained, anemia does not ensue. When red cell destruction exceeds the ability of the marrow to compensate, anemia will occur.

Survey of the 52 patients surviving after valve replacement indicates several ways in which complications may be avoided. Continued improvement in design of valves and close anticoagulant control should be successful in lowering the frequency of embolism. Also, patients receiving anticoagulants must be cautiously observed. Hemolytic anemia should not represent a serious burden as long as surgical techniques allow adequate fixation of the valve without prosthetic insufficiency.

REFERENCES

1. Cartwright, R. S., Palich, W. E., Ford, W. B., Giacobine, J. W., Zubritzky, S. A., and Ratan, R. S.: Combined replacement of aortic and mitral valves: An original transatrial approach to the aortic valve, *JAMA*, 180:6, 7 Apr. 1962.
2. Cartwright, R. W., Smeloff, E. A., Davey, T. B., and Kaufman, B.: Development of a titanium double-caged full orifice ball valve, *Trans. Amer. Soc. Artif. Int. Organs*, 10:231, 1964.

3. Morrow, A. G., Clark, W. D., Harrison, D. C., and Braunwald, E.: Prosthetic replacement of the mitral valve: Operating methods and the results of preoperative and postoperative hemodynamic assessments, *Circulation*, 29:1-2, Apr. 1964.
4. McHenry, M. M., Smeloff, E. A., Davey, T. B., Kaufman, B., and Fong, W. Y.: Hemodynamic results with full-flow orifice prosthetic valves, *Circulation*, 35:1-24, Apr. 1967.
5. Cartwright, R. W., Smeloff, E. A., Cayler, G. G., Fong, W. Y., Huntley, A. C., Blake, J. R., and McFall, R. A.: Total correction of Ebstein's anomaly by means of tricuspid replacement, *J. Thorac. and Cardio. Surg.*, 47:755, June 1964.
6. Smeloff, E. A., Cayler, G. G., and Smith, D. F.: The use of valve prostheses in childhood, *J. Thorac. and Cardio. Surg.*, 51:839, June 1966.
7. Gray, S. J., and Sterling, K.: The tagging of red cells and plasma proteins with radioactive chromium, *J. Clin. Invest.*, 29:1604, Dec. 1950.
8. Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M., and Lawrence, J. H.: Plasma and red cell iron turnover in normal subjects and in patients having various hematopoietic disorders, *J. Clin. Invest.*, 29:1041, Aug. 1950.
9. Wroblewski, F., and Gregory, K. F.: Lactic dehydrogenase isozymes and their distributions in normal tissues, plasma, and disease states, *Ann. New York Acad. Sci.*, 94:912, Nov. 1961.
10. Fink, D. J., Petz, L. D., and Black, M. B.: Serum haptoglobin: A valuable diagnostic aid in suspected hemolytic transfusion reactions, *JAMA*, 199:615, 27 Feb. 1967.
11. Kauder, E., and Mauer, A. M.: The physiology and clinical significance of haptoglobin, *J. Pediatr.*, 59:286, Aug. 1961.
12. Huff, R. L., Elmlinger, P. J., Garcia, J. F., Oda, J. M., Cockrell, M. C., and Lawrence, J. H.: Ferrokines in normal persons and in patients having various erythropoietic disorders, *J. Clin. Invest.*, 30:1512, Dec. 1951.
13. Brus, I., and Lewis, S. M.: The haptoglobin content of serum in hemolytic anemia, *Brit. J. Haemat.*, 5:348, Oct. 1959.
14. Mulder, D. G., Mazzei, E. A., and McAlpin, R. N.: Ball valve replacement for aortic valvular disease, *J. Thorac. and Cardiovas. Surg.*, 52:76, Jan. 1966.
15. Brandenburg, R. O.: Medical problems of aortic valve replacement, *Progr. Cardiovas. Dis.*, 7:531, May 1965.
16. Effler, D. B., Favaloro, R., and Groves, L. D.: Heart valve replacement: Clinical experience, *Ann. Thorac. Surg.*, 1:4, Jan. 1965.
17. Herr, R., Starr, A., McCord, C. W., and Wood, J. A.: Special problems following valve replacement: Embolus, leak, infection, red cell damage, *Ann. Thorac. Surg.*, 1:403, July 1965.
18. Bjork, V. O.: Aortic valve replacement, *Thorax*, 19:369, July 1964.
19. Bjork, V. O., and Malers, E.: Total mitral valve replacement: Late results, *J. Thorac. and Cardio. Surg.*, 48:625, Oct. 1964.
20. McGoon, D. C., Ellis, F. H., Jr., and Kirklin, J. W.: Late results of operation for acquired aortic valvular disease, *Circulation*, 31:1-108, Apr. 1965.
21. Andersen, M. N., Gabrieli, E., and Zizzi, J. A.: Chronic hemolysis in patients with ball-valve prostheses, *J. Thorac. and Cardio. Surg.*, 50:501, Oct. 1965.
22. Dennis, E. W., Johnson, P. C., Kincaid, S. A., Jr., McCall, B. W., Pitzell, E. S., and DeBakey, M. E.: The pattern of RBC survival after prosthetic ball-valve replacement, *Cardiovas. Res. Center Bull.*, (Baylor) Vol. III, p. 62, Oct.-Dec.
23. Brodeur, M. T. H., Sutherland, D. W., Koler, R. D., Kinsey, J. A., and Griswold, H. E.: Red cell survival in patients with aortic valvular disease and ball-valve prostheses, *Circulation*, 30,III,55, Oct. 1964.
24. Stevenson, T. D., and Baker, H. J.: Hemolytic anaemia following insertion of Starr-Edwards valve prosthesis, *Lancet*, 2:982, 7 Nov. 1964.
25. Reed, W. A., and Dunn, M.: Fatal hemolysis following ball-valve replacement of the aortic valve, *J. Thorac. and Cardio. Surg.*, 48:436, Sept. 1964.
26. Pirofsky, B., Sutherland, D. W., Starr, A., and Griswold, H. E.: Hemolytic anemia complicating aortic valve surgery: An autoimmune syndrome, *New Eng. J. Med.*, 272:235, 4 Feb. 1965.
27. Sanderson, R. G., Ellison, J. H., Benson, J. A., and Starr, A.: Jaundice following open heart surgery, *Ann. Surg.*, 165:217, Feb. 1967.
28. Porter, G. A., Kloster, F. E., Herr, R. V., Starr, A., Griswold, H. E., and Kinsey, J. A.: Renal complications associated with valve replacement surgery, *J. Thorac. and Cardio. Surg.*, 53:145, Jan. 1967.
29. Blachly, P. H., and Starr, A.: Postcardiotomy delirium, *Amer. J. Psychiat.*, 121:371, Oct. 1964.
30. Newman, M. M., Hoffman, M. S., and Gesink, M. H.: Mechanical failure of Starr-Edwards aortic prosthesis due to ball fracture, *J. Thorac. and Cardio. Surg.*, 53:398, Mar. 1967.
31. Starr, A., Pierie, W. R., Raible, D. A., Edwards, M. L., Siposs, G. G., and Hancock, W. D.: Cardiac valve replacement: Experiences with the durability of silicone rubber, *Circulation*, 33:1-115, Apr. 1966.
32. Askey, J. M.: Systemic arterial embolism, Grune and Stratton, Inc., New York, 1957.
33. Olesen, K. H.: Mitral stenosis: A follow-up of 351 patients, Ejnar Munksgaards Forlag, Copenhagen, 1955 Thesis, pp. 228.
34. Daley, R., Mattingly, T. W., Holt, C. L., Bland, E. F., and White, P. D.: Systemic arterial embolism in rheumatic heart disease, *Amer. Heart J.*, 42:566, Oct. 1951.
35. Ellis, L. W., and Harken, D. E.: Arterial embolization in relation to mitral valvuloplasty, *Amer. Heart J.*, 62:611, Nov. 1961.
36. Greenwood, W. F., Aldridge, H. E., and McKelvey, A. D.: Effect of mitral commissurotomy on duration of life, functional capacity, hemoptysis and systemic embolism, *Amer. J. Cardiol.*, 11:348, Mar. 1965.
37. McHenry, M. M.: Systemic arterial embolism in patients with mitral stenosis and minimal dyspnea, *Amer. J. Cardiol.*, 18:169, Aug. 1966.
38. Ross, Jr., J., Morrow, A. G., Mason, D. T., and Braunwald, E.: Left ventricular function following replacement of the aortic valve: Hemodynamic responses to muscular exercise, *Circulation*, 33:507, Apr. 1966.
39. Hubis, H. J., and Hultgren, H. N.: Cardiac dysfunction following prosthetic replacement of the mitral valve, *Circulation*, 32:II, 116, Oct. 1965.
40. Peterson, C. R., Herr, R., Crisera, R. V., Starr, A., Brestow, J. D., and Griswold, H. E.: The failure of hemodynamic improvement after valve replacement surgery, *Ann. Int. Med.*, 66:1, Jan. 1967.
41. Cooley, D. A., Bloodwell, R. D., Beall, Jr., A. C., Gill, S. S., and Hallman, G. L.: Total cardiac valve replacement using SCDK-Cutter prosthesis: Experience with 250 consecutive patients, *Ann. Surg.*, 164:428, Sept. 1966.
42. Starr, A., Herr, R. H., and Wood, J. A.: Mitral replacement: Review of six years experience, *J. Thorac. and Cardio. Surg.*, 54:333, Sept. 1967.
43. Yeh, T. J., Anabtawi, I. N., Cornet, V. E., and Ellison, R. G.: Influence of rhythm and anticoagulation upon the incidence of embolization, associated with Starr-Edwards prostheses, *Circulation*, 35:1-77, Apr. 1967.
44. Davila, J. C., Amongero, F., Sethi, R. S., Rincon, N. L., Palmer, T. E., and Lautsch, E. V.: Prevention of thrombosis in artificial cardiac valves, *Ann. Thorac. Surg.*, 2:714, Sept. 1966.
45. Palmer, T. E., Lautsch, E. V., Sanmarco, M. E., and Davila, J. C.: A nonthrombogenic, nonanticoagulant—dependent mitral valve prosthesis, *Circulation*, 35:1-42, Apr. 1967.
46. Braunwald, N. S., and Bonchek, L. I.: Controlled tissue ingrowth on prosthetic cardiac valves: A new means of preventing thromboembolism, *Rev. Surg.*, 23:300, July-Aug. 1966.
47. Cooley, D. A., Nelson, T. G., Beall, Jr., A. C., and DeBakey, M. E.: Prosthetic replacement of cardiac valves: Results in 242 patients, *Dis. Chest*, 46:339, Sept. 1964.
48. Duvoisin, G. E., Brandeburg, R. O., and McGoon, D. C.: Factors effecting thromboembolism associated with prosthetic heart valves, *Circulation*, 35:1-70, Apr. 1967.
49. Gadboys, H. L., Litwak, R. S., Niemetz, J., and Wisch, N.: Role of anticoagulants in preventing embolization from prosthetic heart valves, *JAMA*, 202:282, 23 Oct. 1967.
50. Sproule, B. J., Mitchell, J. H., and Miller, W. R.: Cardiopulmonary physiological responses to heavy exercise in patients with anemia, *J. Clin. Invest.*, 39:378, Feb. 1960.
51. Hutt, M. P., Reger, J. F., and Neustein, H. B.: Renal pathology in paroxysmal nocturnal hemoglobinuria: An electron microscopic illustration of the formation and deposition of ferritin in the Nephron, *Amer. J. Med.*, 31:736, Nov. 1961.
52. Reynolds, R. D., Coltman, Jr., C. A., and Beller, B. M.: Iron treatment in sideropenic intravascular hemolysis due to insufficiency of Starr-Edwards valve prostheses, *Ann. Int. Med.*, 66:659, Apr. 1967.
53. Walsh, J. R., Brodeur, M. T. H., Ritzmann, L. W., Sutherland, D. W., and Starr, A.: Urinary iron excretion in patients with prosthetic heart valves, *JAMA*, 198:505, 31 Oct. 1966.
54. Sigler, A. T., Forman, E. N., Zinkhorn, W. H., and Neill, C. A.: Severe intravascular hemolysis following surgical repair of endocardial cushion defects, *Amer. J. Med.*, 35:467, Oct. 1963.
55. Stahlman, F., Sarnoff, S. J., Case, R. B., and Ness, A. T.: Hemolytic syndrome following the insertion of a lucite ball valve prosthesis placed in the cardiovascular system, *Circulation*, 13:586, Apr. 1956.

Renal Dialysis Center Operational Plans

BENJAMIN H. BARBOUR, M.D., JOHN E. MEIHAUS, M.D., THOMAS
BERNE, M.D., AND EUGENIA ORRELLANA, B.S., *Los Angeles*

■ *The Southern California region has available a Renal-Dialysis Center at the University of Southern California School of Medicine and the Los Angeles County General Hospital. The center is prepared to carry out dialysis, transplantation, research and education in nephrology.*

Patient selection for dialysis will be randomized among optimum candidates.

The high cost of dialysis per patient might be reduced through home dialysis and by successful homotransplantation. The center plans to arrange transplantation of cadaver kidneys matched by tissue typing to a recipient undergoing hemodialysis. Such an approach will keep a constant turnover of patients and will help in research efforts toward better understanding of problems in nephrology.

SHORTLY AFTER THE demonstration of successful therapy by chronic hemodialysis, it became apparent that a community hemodialysis center might be the best method of making available life-saving dialysis techniques. Through foundation support as early as 1961, and support from the U.S. Public Health Service in 1964, several hospital-based dialysis units were established.^{6,7} In September 1965, a State of California Assembly bill to establish two renal dialysis centers in California was made law.¹ Soon afterward a feasibility study was begun and the results of this study indicated that more facilities were needed and were within the capacity of the State to provide.² In October 1966, the Los Angeles County General Hospital and the University of Southern California School

of Medicine were selected as operators for a Southern California center.

As the money for personnel, remodeling and equipment was obtained by matching funds (two-thirds Vocational Rehabilitation funds; one-third State Department of Public Health funds), it was necessary to negotiate a tripartite contract between the State Department of Vocational Rehabilitation, the State Department of Public Health and Los Angeles County. The contract had to conform to Federal rehabilitation standards since the State Department of Rehabilitation obtained its funds from the Federal agency. For operational funds, a contract between the State Department of Public Health and Los Angeles County was negotiated. These contracts were completed in February 1967.

The primary goal of the center is to provide specialized and comprehensive medical care to patients handicapped by chronic renal failure through a hospital-based center and through center-supervised home dialysis. The hospital-based center will be prepared for hemodialysis proce-

From the Departments of Medicine and Surgery, University of Southern California School of Medicine, and Los Angeles County-University of Southern California Medical Center, Los Angeles.

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Reprint requests to: Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033 (Dr. Barbour).

dures within the hospital and for transplantation activities. Secondly, support will be provided for research and education. First a strong and stable hospital-based program will be established, and it is anticipated that once an experienced staff has developed, home dialysis programs and dialysis services in outlying hospitals will evolve.

The Renal-Dialysis Center is viewed as an integrated component within the Los Angeles County General Hospital and the University of Southern California School of Medicine. The relationship of the major functions of the center to other elements of the hospital and the community have been considered to be of paramount importance in planning the center's activities. One of the first problems which has required detailed analysis is that of selecting patients. Several studies have shown that there are large numbers of patients in the community who need treatment. Estimates of as many as 1,700 new cases a year in California have been made.² In the Los Angeles County General Hospital in the period 1963 to 1965, 45 patients a year died who might have been rehabilitated by chronic dialysis.⁵ The present facility plans to build gradually to constant load of 30 patients over the fiscal year 1967 to 1968. As there will still be large numbers of patients who will remain untreated by hemodialysis, the problem of selection is a pressing one.

The question of selection has been dealt with in several ways by different groups in other parts of the country. In some places it is first come, first served until the limit is reached.⁸ Others use a complex board of laymen and physicians to make the decisions.⁴ The Southern California Center has a Patient Selection Committee made up of representatives as follows: The director and the assistant director of the center, a member of the Department of Medicine and of the Department of Psychiatry, USC School of Medicine, a social

service representation from the Department of Social Service of the Department of Hospitals, Los Angeles County, a physician representing the Los Angeles County Medical Association, one representing the Southern California Kidney Foundation. Any patient referred by a licensed physician in the State of California will be accepted for evaluation by the professional staff of the center. The patient's medical, psychiatric and sociologic history will be reviewed and the patient will be judged to be either an optimum or alternate candidate largely on the basis of medical findings.

An optimum candidate is a patient who is disabled because of chronic renal insufficiency and who does not have any other disabling illness or significant organ involvement. Patients who have had cerebrovascular accidents with paralysis, severe coronary artery disease and heart failure or another disabling systemic disease, or who show unwillingness to cooperate with the prescribed hemodialysis program, are examples of alternate candidates. Each time an opening occurs on the program, all referrals will be classified into one or the other category. The group of optimum candidates will be pooled and one of them will be selected by lot for therapy. If there are no optimum candidates, then the alternate pool will be used to draw the patient for treatment.

Criteria for separation into these two categories are admittedly imperfect because of defects in the completeness of knowledge about the nature of chronic renal insufficiency as it relates to other systems and because of the moral and philosophical implications underlying the use of psychological and social factors for patient selection. The Patient Selection Committee felt that a degree of randomness was the only way out of this current dilemma. Still, it is important to give patients who have the greatest potential for rehabilitation the best chance. If a candidate is free of other dis-



PATIENT FLOW THROUGH DRC

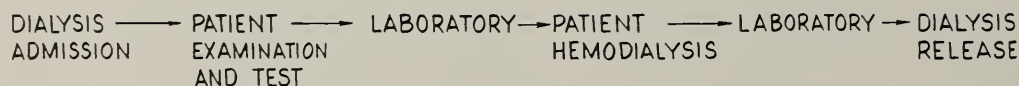


Chart 1.—Patient flow charts show, *top line*, major activity during patient work-up; *lower line*, major activity during patient treatment.

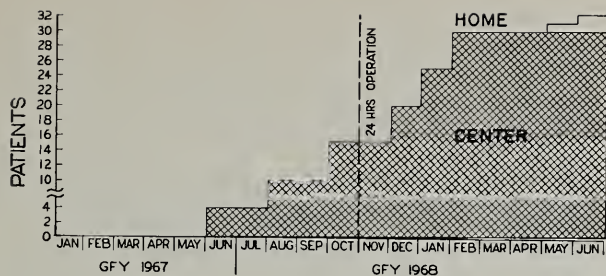


Chart 2.—Rate of accumulation of dialyzed patients. (GFY==Government Fiscal Year.)

abling illness, it is assumed that his potential is greater for rehabilitation than that of a patient who has another disability. On the other hand, the alternate candidate will not be absolutely excluded from therapy, as he might be selected if there are no optimum candidates available.

Once a patient is selected, operation to prepare for cannulation will be completed and the patient will be treated one or more times weekly in the center. Chart 1 shows the patient flow activity for each treatment. On the dialysis day, each patient will proceed directly to the dialysis center. The essential paper work associated with the hospital admissions will be eliminated, since the patient will fit into a well defined schedule. If it becomes necessary to put a patient in hospital for treatment of complications, he will be housed on an appropriate ward between treatments.

Chart 2 shows the schedule for acceptance of patients. The first patients were selected in June 1967. Thereafter, a few additional patients were added every month or two until a maximum of 30 patients was reached. Home training then was begun and the first home-dialysis patient is now treating himself at home.

The floor plan of the center, which is situated on the fourth floor of the main building at Los Angeles County General Hospital, is shown in Figure 1. The center is designed to integrate the institution's renal service with the dialysis activity.

Cost of Treatment

The cost of treatment is a matter of critical concern. Estimates of costs of dialysis vary greatly from center to center. In the Seattle Artificial Kidney Center where cost analysis has been carefully carried out, the average per patient per year is \$10,317.84.⁹ An estimate of \$11,496.16 per patient per year has been made by the Southern California Center. Since personnel costs make up the major portion of the expense of dialysis, home

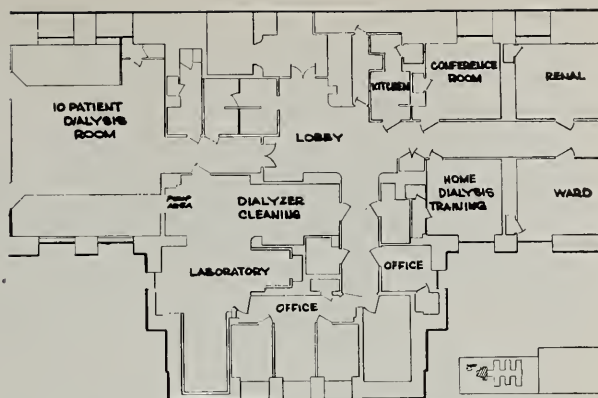


Figure 1.—Floor plan of Renal Dialysis Center.

dialysis, which makes relatively little demand on professional personnel, may further reduce the cost. However, it is not clear yet whether only a select few can be treated by home dialysis. It must be borne in mind, however, that if dialysis is used to support transplantation, then a hospital dialysis center will be required. Another prospect for cost reduction is to train medical assistants to carry out dialysis in outlying community convalescent centers. So long as these assistants have a major medical center that they can turn to for help if need be, they probably can serve many patients without tying up valuable space at the center.

The plans for patient payments for dialysis treatment in the center are still being formulated. Each patient selected for therapy will be interviewed to determine his financial resources. If he has medical insurance or is eligible for governmental medical assistance, efforts will be made to apply this support to the cost of dialysis. If there are no third-party payments involved, a plan of payment will be negotiated between the patient and the center. Arrangements will be made in such a way as to avoid great financial hardship for the patient or his family.

In light of the high cost of dialysis, the physical and functional restrictions placed on patients and the limited numbers of patients that can be dealt with, an alternate method of therapy is obviously desirable. Homotransplantation may be one alternative, particularly in view of recent information on cadaver transplants and tissue matching techniques.^{3,10} A logical approach to coping with the large numbers of patients is to provide a combination dialysis-transplant program. Such a program might be most successfully operated by classifying each dialysis patient through immuno-tissue typing. Then as cadaver kidneys become

available, a recipient could be selected by type-matching. With large numbers of patients undergoing dialysis, the chances of a good match from random cadaver donors would be high.

Undoubtedly, there will be new developments which will alter the current operational plans. The center will constantly seek new methods, techniques and ideas which will improve the understanding of renal disease and aid in amelioration or cure.

REFERENCES

1. Assembly Bill No. 2202, State of California 17 Sept. 1965.
2. California State Department of Public Health: The Feasibility of

Chronic Hemodialyses in California, Volumes I and II, Berkeley, California, June 1966.

3. Hill, R. B., Dahrling II, B. E., Starzl, T. E., and Rifkind, D.: Death after transplantation, *Amer. J. Med.*, 42:327, 1967.

4. Lindholm, D. D., Burnell, J. M., and Murray, J. S.: Experience in the treatment of chronic uremia in an out-patient community hemodialyses center, *Trans. Amer. Soc. Artif. Intern. Organs*, 9:3, 1963.

5. Los Angeles County General Hospital Survey: Unpublished observations.

6. McDonald, H. P., Hessert, R. T., Thomson, G. F., Waterhouse, R. K., and Friedman, E. A.: Design, equipment and function of a fifteen-bed hemodialyses unit, *Trans. Amer. Soc. Artif. Organs*, 12:370, 1966.

7. Murray, J. S., Tu, W. H., Albers, J. B., Burnell, J. M., and Scribner, B. H.: A community hemodialysis center for the treatment of chronic uremia, *Trans. Amer. Soc. Artif. Intern. Organs*, 8:315, 1962.

8. Retan, J. W., and Lewis, H. Y.: Repeated dialyses of indigent patients for chronic renal failure, *Ann. Intern. Med.*, 64:284, 1966.

9. Seattle Artificial Kidney Center: Personal communication, 1967.

10. Terasaki, P. I., Vredevoe, D. L., and Mickey, M. R.: Serotyping for homotransplantation X, *Transplantation*, to be published.

TELLING PARENTS ABOUT INTERSEX PROBLEMS

What does one tell parents when removing ovary of newborn with intersex problems?

"I have found a neat little way of overcoming this which I have found to be successful in all of my cases so far. When we come down from the operating room and the parents are anxiously waiting to know what we found in their daughter and what was done, we say that we found that their child was born with abnormalities of her sex glands, or gonads if they're more sophisticated, without using the word ovary or testis. Then we say that because this abnormality of their gonads frequently leads to tumors and hernias and serious complications, it was necessary to remove the gonads. This I've been always able to get away with; nobody has ever pinned me down on what I mean by the gonads or sex glands. They assumed that their daughter had ovaries, and it was necessary to remove them because of possible tumor formations."

—ABRAHAM E. RAKOFF, M.D., Philadelphia
Audio-Digest *Obstetrics and Gynecology*, Vol. 15, No. 3

The Reporting of Cytologic Smears

Selected Problems with Morphologic Terms

DUANE N. TWEEDDALE, M.D., *Lexington, Kentucky*

■ *Problems arise when morphologic terminology falls into categories which: (1) Utilize numbers to replace words and (2) utilize words of such indeterminate meaning that definition depends entirely upon local usage.*

We should strive to replace any means of diagnosis that does not convey specificity with means capable of precision. The major criterion for the suitability of a diagnostic system is that it is universally understood and is precise enough to result in optimal patient management. Meeting those demands requires the use of nomenclature in cytology that approximates, as far as possible, the actual tissue diagnosis.

MORPHOLOGIC TERMS currently in use do not always mean precisely the same thing to the person who utters them as they do to the person who hears or reads them. Particularly in cytology there are numerous communications gaps. Much of the fault lies in the fact that the field of cytology is a relatively new one that is constantly growing and maturing under skillful leadership. In this regard it is noteworthy that of 142 definitions in the American Society of Clinical Pathologists *Cyotechnology Manual*, at least three are not found in a recent edition of *Dorland's Medical Dictionary*.

A by-product of maturation is reassessment and, at times, modification of original concepts as well as the development of new ideas to replace those found to be inadequate. Often, the change requires translation into new definitions. For example, the term *cornified cell* was replaced by *eosinophilic*

(*karyopyknotic*) *superficial cell*, and the term *acidophilia* replaced by *eosinophilia*. A major change is related to terms employed in reporting the cytologic smear. Almost everyone is familiar with Papanicolaou's original classification of I to V but there are numerous other methods of reporting. In fact the variation in cytology report forms is staggering, bearing witness to the state of flux in this field. Some methods of reporting contain terms far too ambiguous for general use.

The numerical system of reporting, proposed by Papanicolaou in the infancy of exfoliative cytology, has been referred to as the "numbers game." Nevertheless, that means of reporting served a very useful purpose in the early years of this method of cancer detection. In some quarters, the class system of reporting persists. Without doubt the most significant area of confusion arises with smears reported as Class III. Such a report subsequently may be proved to represent a gamut of lesions ranging from those which are perfectly benign to those of unquestionable malignancy. In some

From the Department of Pathology, University of Kentucky, College of Medicine, Lexington, Kentucky.

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Reprint requests to: Department of Pathology, University of Kentucky College of Medicine, Lexington, Kentucky 40506.

series² smears so reported were shown to be associated with malignancy in 15 percent of cases, while in others¹ Class III smears were subsequently shown to be about equally divided between benign and malignant lesions.

Why is there such a divergence of results among those using the same numerical method of reporting? Perhaps the material studied varied from laboratory to laboratory. For example, if a single slide prepared from material from the vaginal pool is compared with slides of exudate from the pool, of cervical scrapings and of endocervical aspiration, ordinarily it will be found that the overall diagnostic accuracy is far superior with the latter. Also, fractionated cytology specimens submitted by an experienced physician may aid greatly in clarifying a "gray zone" smear. This especially is true in our institution, where medical students often take cytologic specimens. When material is taken by experienced staff members, it is usually of superior quality and slides labeled as to origin of material may direct attention to a specific area which will give optimal biopsy results. Obvious difficulties still may be encountered, since neoplastic cells may be carried over from one area to another in the sampling process. A refined diagnosis not only is made by the observation of a few malignant cells, but also by determining the patterns such cells make on the slides, then integrating that knowledge with information concerning the site from which the smear was taken and with pertinent historical data.

Another factor of obvious importance in accurate reporting is the experience of the cytologist. With experience, the number of equivocal reports diminishes. In this regard, experience at our own institution may be enlightening. There we see a large number of women who have been treated for cervical cancer by means of radiation. In the course of follow-up examinations, many cytologic smears are seen for evaluation. At first, when our experience with such smears was limited, we had frequent borderline reports which we felt contributed little toward better patient care. After studying a fairly large series of such examinations, we gained a higher level of confidence and experienced a significant decrease in equivocal reporting. Similarly, the dramatic patterns observed in immediate or early post-partum smears were defined by a comparable study. I do not believe that experience comes merely by looking but by evaluating what one sees. All of our positive smears, both dys-

plastic and cancerous, are kept in limbo in a special packet awaiting biopsy material. Each month these cases are subjected to a comprehensive review, at which time we attempt to correlate our findings.

What about those "Class III" diagnoses? Are we talking about a matter of clinical importance? In general, about 1 percent of an initially screened population will be found to have *in situ* or invasive cancer and a slightly lesser proportion dysplasia. If 5 to 6 percent of reports are Class III, it is evident that a fairly large number of women not only will have needless anxiety but will be put to added expense. Thus, it is of more than academic interest to narrow the gap. I do not know how narrow the cytologic gap between benign and malignant can become. No doubt there will always be a gray zone in reporting related largely to the enormity of the biologic spectrum and the existence of transitional stages between benign and malignant lesions.

I feel that many patterns are so diagnostic of cancer that one is doing a disservice if he does not come right out and say "cancer positive." Recently we have had a few cases with unquestionably positive cytologic smears following hysterectomy for *in situ* carcinoma of the cervix. In two instances, subsequent biopsy of material from the upper vagina was negative. Upon our insistence, further biopsy, taken from lower in the vagina revealed *in situ* cancer.

Unfortunately, there are numerous other examples of inadequate terminology. For example, some hospitals in London do not class or report smears to correspond with tissue diagnosis but grade them I to V. This causes confusion with histopathologic grading. Some laboratories use the word inconclusive in reporting cytologic material. According to Webster, the term means: leading to no conclusion or not leading to definite results. What it means in cytology reporting most certainly must be by local definition. I am convinced that the term *inconclusive* does not give the same diagnostic message to all who receive it. Should we not consider abandoning such a word? The terms *suspicious* and *suggestive* appear to fall in the same category as *inconclusive*. Because the terms do not have universal meaning and are defined according to local custom, their usefulness is impaired.

REFERENCES

1. Hall, J. E., and Rosen, I. H.: Significance of the Class III cervical smear, *Am. J. Obstet. Gynec.*, 79:709, 1960.
2. Smith, C. W., and Sealey, R. M.: The clinical significance of Class III cervical Papanicolaou smear, *Amer. Surg.*, 28:420, 1962.

The Educationally Handicapped Child

The Physician's Place in a Program to Overcome Learning Disability

DOROTHY COLODNY, M.D., CAROLYN KENNY, M.A., AND L. F. KURLANDER, M.D., *San Diego*

■ *Under California Assembly Bill 464, special classes may be provided by school districts for children designated as educationally handicapped. An educationally handicapped child is not mentally retarded or physically disabled. He may have neurological handicap or emotional disorder, but he must show impaired achievement in relation to his tested abilities.*

A physician may be asked to participate in the program, either as a specified member of the admissions committee of the school district or to provide a medical clearance for entrance of one of his own patients into the program.

He does a thorough history and physical examination but adds special examination of attention, activity, coordination and attitudes.

The educationally handicapped child is helped most by the physician who does not reject the idea of educational handicap even if the medical examination is negative; who treats his minor ills; who medicates, when it is indicated, for hyperactivity, distractibility or extreme anxiety; who cooperates with parents and school personnel.

CALIFORNIA PHYSICIANS whose practice includes school-age children have a new opportunity to be of service to their young patients and to the community. The Programs for the Educationally Handicapped were established in 1963 by the California Legislature under Assembly Bill 464, which specifically requests physician participation. Many physicians are uncertain just what is wanted of them. We can define the physician's function precisely within his capabilities, so that he may

make an independent and valuable contribution to a multidisciplinary effort.

The development and passage of the legislation resulted from a need for special provisions for the education of children with learning handicaps due to behavioral or neurological disorders. The Education Code defines educationally handicapped minors as "... minors other than physically handicapped minors or mentally retarded minors who, by reason of marked learning or behavioral problems or a combination thereof, cannot receive the reasonable benefit of ordinary education and facility." (Education Code Section 6750)¹⁴

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Reprint requests to: 3695 Third Avenue, San Diego 92103 (Dr. Colodny).

This definition was further interpreted in Article 27 of Title 5 of the California Administrative Code, Section 221a: An educationally handicapped minor, eligible for admission to a program, is a minor described in Education Code 6750 whose learning problems are associated with a behavioral disorder or a neurological handicap or a combination thereof and *who exhibits a significant discrepancy between ability and achievement*.

This is not a mandatory program and whether or not a program is to be developed in an individual district is up to the district. Parents' consent is required before a child can be referred.

The program requires a highly individualized approach involving specialized techniques, requirements, equipment and environment to cope effectively with the complex learning characteristics and problems of the educationally handicapped student.¹² For many of these pupils, changes in behavior are required before effective learning can occur. Reduction in anxiety, overcoming fear of failure, controlling of impulsive behavior and learning self-control are important factors that facilitate learning. Many of the children will require additional assistance in such areas as visual and auditory perception, spatial orientation, physical coordination, motor skills, communication skills, language development and concept formation.⁹ The ultimate goal is to return the pupil to full-time regular classes.

Children are identified principally by their teachers, but may be referred also by school psychologists, school nurses, private physicians, and even by parents. Selection procedures are carefully prescribed. Usually the concerned teacher, who has had the opportunity of working closely with the child in the classroom and has intimate knowledge of his difficulty, with parental permission, refers the pupil for study by the school psychologist. A medical study is required also, and it is usually done by or through the family physician, with referral to other specialists as he sees fit. A medical report form set up specifically for this study, is sent by the school to the physician. It has been found to be helpful in calling attention to the difficulties needing special remediation.³

Each school district appoints an admissions committee composed of a teacher, a school nurse or social worker, a school psychologist, a principal and a licensed physician with experience in working with children and representing, but not limited to, such fields as pediatrics, neurology and psy-

chiatry. Members of this committee review the data submitted by the teacher, psychologist and the child's physician and determine whether his interest would be served by admission to the program.

Their charge is not to make a medical diagnosis, but an educational one, supported by psychological data, classroom observation and medical information. We must emphasize that the Program for Educationally Handicapped Minors is not a medical program, but an educational plan. Educators know from experience and from research studies that children with emotional problems and those with neurological handicaps profit from the identical remedial approach, so that a definitive diagnosis of either disorder is not required.¹³

The physician asked for a medical report to the admissions committee can approach this in two ways.

He can diagnose whatever degree of developmental, neurological or psychiatric deviation he sees in the child and report his purely medical opinion; or, broadening his horizon, ask for information from the school and the psychologist, correlate this with his own findings, explore the learning disorder as far as he is able, confer with the school personnel and, additionally, make recommendation as to the child's eligibility for the class and for his best management in it. If he does the latter, it is not beyond his capacity to make a diagnosis of educational handicap.

Sometimes physicians have felt obliged to rule in or out the presence of neurological handicap (more officially designated these days as minimal cerebral dysfunction) or emotional disorder. It must be noted at once that this is not in the actual request to the family physician or pediatrician; the request is for a medical clearance alone. Of course, as physicians concerned with the detection of physical and emotional disorder, they may feel a responsibility to go as far as they can in this direction. But time and training may not always make that possible. Likewise, if the child's parents wish, the physician can try to treat the disorder he finds, as well as any concurrent conditions which may contribute to the patient's trouble in attention or learning.

Much time and discussion are spent on this matter of minimal cerebral dysfunction, neurological handicap, "hyperactivity syndrome," "brain damage," a peculiar constellation of symptoms¹⁶ involving the province of educators, psychologist and various physicians. Space does not permit a dis-

cussion of this disorder except as it applies to the screening problem. Most usefully, we can refer readers to the preliminary Report of Task Force I of the Project on Minimal Brain Dysfunction in Children, Monograph No. 3 of the National Institute of Neurological Diseases and Blindness. This study is a very careful and condensed report on "terminology and identification" of the child with this syndrome.⁶ It will be followed by further research. In its present form, it presents an excellent summary of symptoms and guidelines as to the possible areas of exploration for the practitioner. The ten most frequent characteristics are cited.

The term "minimal cerebral dysfunction" was selected in part to avoid the assumption that one is dealing with "damage" to an anatomical locus in the brain. It is important not to become defensive if, for want of better terms, parents, teachers and other laymen approach the physician with talk about "brain damage" or other expressions of the pseudoscientific jargon current on this subject.

The real concern is with the child's equipment for learning, his ability to process, store and recover information appropriately. Clinically, it can be broken down into a review of his sensory equipment, his attention, his communication skills (listening, speaking, reading, writing), his perceptual apparatus, not only visual but auditory, his memory, and his higher thinking functions of abstraction and comprehension.¹ One must note his feelings about learning and about himself as a learner.² His parents' abilities and attitudes are relevant, too.

In actual office practice, few physicians can conduct this entire study alone, but all must, as a minimum, take an adequate history, do a careful physical examination and make some specific neurological observations; they may need an electroencephalogram if impaired or interrupted consciousness disables the child. They should note the child's attention, activity, motility, mood, temper, gross and fine coordination and expressed attitudes.¹¹

It is most important not to come to negative conclusions because of the paucity of evidence on examination. Many physicians have discounted the seriousness of a child's problem because on physical and, especially on classic neurological examination, the findings are negative. One must not minimize the evidence of a carefully taken history which explores the child's prenatal and para-

natal experience, his minor developmental deviations, his habit patterns and the expressed opinions of those who live with him. The teacher or principal may offer valuable observations, though they may not be tangible. Any child, and especially an educationally handicapped child, may function with great variability, both from one day to the next and in different situations.¹⁶ This variability is one of the diagnostic signs of a child with learning problems. Physicians have been criticized¹⁵ for denying that a problem exists, saying "nothing is wrong with him" because a child is quiet, underactive and docile on Tuesday in his office, although on Monday at school he was irritable, hyperactive and rebellious. It is odd that some negate this kind of historical data about learning or behavior when they rely so heavily on history in the absence of present signs and symptoms in peptic ulcer or allergic disease or angina.

A single test or a single kind of reading test may give a false impression of a child's reading ability.^{5,10} Only a competent educational specialist can really tell if a child's ability to read is as useful to him as it should be.

Likewise, the fact of emotional disorder does not necessarily mean that the learning problem is "all emotional" or even primarily emotional, or that a referral for psychiatric care should be made before or instead of special school placement.⁸

It is also necessary to keep in mind that the children in a class for the educationally handicapped do not represent a single disability. Learning can be grossly impaired by a spectrum of handicaps which disable the child who is hyperactive, distractible and explosive, and also the one whose only abnormality may be an apparently pure reading disability.⁷

One of the physician's major responsibilities is his ability to influence parents by his professional authority. This force may decide whether parents will accept a remedial placement offered their child by the school. It is not suggested that physicians blindly accept the recommendations of teachers or psychologists. They can inform themselves as to the precise provisions of the law. Each can try to learn if and how the program is operating in his district, can appraise the professional competence of the available teachers and determine which children the particular program best serves. The physician who has done that will be better able to counsel both the parents and the

school on the advisability of a child's placement, as well as his eligibility.

Many times school and parents feel that the physician can continue his services to the child after the school placement is made. This ongoing aid consists of four things: 1) continued interest and reevaluation of the child, 2) possible specific medication if the physician feels the patient requires it, 3) treatment of the child's minor ills, and 4) ongoing support to parents, child and teacher for the best use of the program.

Many of the children are under the care of specialists for their neurological or psychiatric ailments. Parents who are unwilling or unable to arrange this, or whose children are not so ill, turn to the family physician or pediatrician, asking for medication for hyperactivity, distractibility, irritability. Many times these requests are refused, sometimes because the physician feels they have been instigated by non-medical personnel such as teachers, principals and psychologists. Naturally he will not prescribe a drug without coming to independent conclusions that it is necessary.

More and more studies show, however, that excellent results with neurologically handicapped and emotionally disturbed children can be obtained by a combination of special teaching methods and judicious medication.⁵ Contrary to the belief of many, psychotherapy is rarely the treatment of choice. The careful administration of drugs as an aid to a child's comfort and efficiency in the classroom is usually greatly appreciated by the child, by his parents and by his teacher.⁴ The teachers often express interest in cooperating with the physician in this regard; with the parents' permission, they ask to be informed of the medication and what it can be hoped to do. They are usually willing to make very helpful observations and reports on its efficacy. This can be a very rewarding mutual collaboration.

Since most of these children have more than one problem, it is vital that the physician and school and any other aides remain in touch and that face-to-face conferences, if possible, be held to decide what is the most fruitful order of help for the child.¹⁰ Otherwise, the patient may be over-scheduled with referrals for visual training, tutoring and motor training, at the same time that many of the difficulties for which such training is needed

are being approached in a more organized way in school.

Another area of service lies in the identification and treatment of minor ills and discomforts. Because the educationally handicapped child often has problems of attention, it is important that he not be distracted from his schoolwork by his bodily sensations. The chronic sniffer, itcher or acher is entitled to relief of these sensations which he is less than normally able to ignore. This aid need not necessarily be regarded as "coddling" or as predisposing to hypochondriacal interest. Rather, the relief of minor distractions frees the child's energy for his real business of learning in school. Physicians are sometimes provoked by the insistence of parents and other laymen that they treat symptoms they have regarded as trivial in the past; sometimes a graceful concession will be needed.

But it is certain that all who work with learning problems of children wish only to further the child's ability to learn and grow. This program, if we participate properly, gives us a chance to learn and grow in our own ability to do so, while we await the results of further medical and educational research.

REFERENCES

1. Anderson, Ursula M.: Reading disability, *J. School Health*, XXXV:145-158, Apr. 1965.
2. Bennett, E. Muriel: The pediatrician's role in evaluating the child with a learning disability, *Academic Therapy Quarterly*, 1:129-138, Spring 1966.
3. California Association of School Psychologists and Psychometrists and California State Psychological Association: The Role of the Psychologist in the Educationally Handicapped Program, 1965.
4. Colodny, Dorothy, and Kurlander, LeRoy F.: Panacea, palliation or poison: the psychodynamics of a controversy, *Amer. J. Psychiat.*, 121:1168-70, June 1965.
5. Clements, Sam D., and Peters, John E.: Minimal brain dysfunction in the school age child, *Arch. Gen. Psych.*, 6:17-29, Mar. 1962.
6. Clements, Sam D.: Minimal Brain Dysfunction in Children, Department of Health, Education and Welfare, 1966.
7. Clements, Sam D., and Peters, John E.: Diagnosis and treatment of minimal brain dysfunction in the school age child, *Feelings*, 8: p. 1, Sep. 1966.
8. Doll, Edgar A.: Education and the Interjacent Child, Vanguard School, Haverford, Penn., 1965.
9. Flower, Richard, Gofman, Helen, and Lawson, Lucie: Reading Disorders, F. A. Davis Co., 1965.
10. Hammond, Keith, and Keitel, Hans: Childhood academic underachievement, *Medical Science*, 62-65, Dec. 1966.
11. Hellmuth, Jerome: Learning Disorders, 2 volumes, Hellmuth and Straub, Seattle, 1966.
12. Mahler, Don: Programs for Educationally Handicapped Pupils, California Association for Neurologically Handicapped Children, 1966.
13. O'Reilly, Robert A.: Classes for neurologically handicapped children, *Childrens House*, 16-17, Nov./Dec. 1966.
14. Rafferty, Max: California's Program for Educationally Handicapped Minors, California State Department of Education, 1966.
15. Solomons, Gerald: The school problem and the private practitioner, *Medical Times*, 93:147-152, Feb. 1965.
16. Thompson, Alice C.: Educational Handicap—A Handbook for Teachers, Associated Clinics, California State College, Los Angeles, 1966.

Statistics on Stroke

A Pilot Study of the Clinical Evidence Justifying the Reporting of Stroke on Death Certificates in Alameda County, California

BRUCE S. SCHOENBERG, M.D., *Bethesda, Maryland*, AND
JAMES MEYERS POWELL, JR., M.D., *Chapel Hill, N. C.*

THE MAGNITUDE OF the stroke problem is to some extent reflected in the fact that stroke ranks third as a cause of death in the United States, and that in 1962 the total economic cost of strokes to the nation as estimated in *The President's Report* stood at \$1.1 billion.⁷ Furthermore, while in 1963 some 80 percent of the stroke deaths occurred in people aged 65 and over, stroke also claimed 38,337 persons under 65.¹⁰ A reliable estimation of the extent of the stroke problem is necessary to provide a basis for judging changes in stroke mortality and thereby more effectively evaluate preventive and therapeutic techniques.

Mortality data seem to be a ready source of such information, but problems such as the accuracy of diagnosis, the completeness of reporting, and whether stroke is coded as the underlying cause of death when several pathological conditions are contributing to the death of the patient make it difficult to obtain reliable estimates of mortality from stroke. A number of reports concerned with the epidemiology of stroke have made use of the information contained on death certificates.^{1,4,9,12-14} The value of such studies is, however, a direct function of the reliability of the information on the death certificate. The most extensive analysis which has been made of death

certificate information in the United States was carried out in Pennsylvania by Moriyama and coworkers in 1958.⁶ These investigators did not confine their interest to cerebrovascular accidents, although they did include this group of diseases among the several which they studied. They did not explicitly state their criteria for the evaluation of the quality and certainty of diagnosis, and although they did estimate the frequency with which persons who die of conditions other than stroke are falsely assumed to have died of stroke, they did not record the frequency with which actual stroke deaths are reported as having been due to other causes. In other words, they estimated the false positive rate, but not the false negative rate.

This paper reports on a pilot study, in which a very small sample of death certificates is analyzed according to neurological criteria, which together with the diagnosis appearing on the clinical record form the basis of estimating false positive and false negative rates of diagnosis listed on the death certificate. The study was designed to answer the following questions:

- *Problem of false positives:* Has a diagnosis of stroke been entered on the death certificate without any apparent justification, as judged by the patient's previous history (obtained from hospital, nursing home or coroner's records)?

- *Problem of false negatives:* In cases where stroke is not mentioned on the death certificate, has a stroke occurred as judged by the clinical evidence or mention of stroke in the patient's previous history?

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• In the case of true positives, what proportion appears in the tabulation of vital statistics, which, of course, uses only one diagnosis from each certificate?

Material and Methods

Cases: The sample was drawn from copies of death certificates issued in Alameda County, California, in April, 1965. In all, there were 94 certificates in which stroke was listed as the immediate cause of death, as one of the underlying causes of death, or as a contributory cause of death. Of these, 87 concerned deaths which had occurred in medical institutions, and seven concerned deaths at home. Since the time for field work was very limited, it was necessary to restrict our attention to cases in which death occurred in a medical institution (hospital or nursing home) in which more than one such death had occurred. This meant that 28 certificates were omitted from the sample. Of the remaining 66 certificates, one more had to be excluded because no clinical record was available. These details are summarized in Table 1.

Controls: A control group was selected by matching each certificate in the stroke series with another in which the underlying cause of death had been coded under the hypertensive and cardiovascular diseases, rubrics 420-459 of the *International Classification of Diseases*, 1955 Revision.¹¹ Throughout this report, the coded underlying cause of death refers to the one coded by Alameda County and is not necessarily the one appearing in the national statistics. The matching was done on the basis of age, sex, race and place of death (hospital or nursing home). Categories

420-459 were chosen as the non-stroke group among which the majority of false negatives might occur, because after an examination of the death certificates in the stroke group (rubrics 330-334), it was found that cardiovascular and hypertensive diseases are the conditions most often associated with stroke on death certificates. This was not surprising since it is a long established medical fact that cerebral hemorrhage is a complication of hypertension,⁸ and it has recently been shown that cerebral thrombosis is most likely to occur in persons who already have hypertension or electrocardiographic abnormalities.⁵ This particular set of controls would therefore increase the chances of finding evidence for stroke in the medical records although stroke was not mentioned on the death certificate. In other words, our selected non-stroke group was biased toward a higher proportion of false negatives than the general non-stroke population that had died in Alameda County in April, 1965.

Record Abstraction

In consultation with Dr. William Drake of the University of California School of Medicine and Dr. John Cutler of the University of California School of Public Health, a series of criteria was drawn up which would serve as a basis for deciding whether a diagnosis of cerebrovascular accident appeared to be justified. Further details of these criteria are listed in the appendix.

Results

The following definitions were used to determine the presence or absence of stroke by reference to the clinical record: 1) determined by our own criteria and 2) named as such on the hospital or nursing home chart.

False positives were considered to be cases in which stroke was listed as such on the death certificate, but which did not meet our own criteria (definition 1, see Table 2) or in which stroke was not mentioned as a diagnosis on the medical record (definition 2, see Table 3). Tables 2 and 3 show how many false positives and false negatives were found in relation to whether the death occurred in a hospital or a nursing home. In reference to definition 1, there was one (2 percent) false positive in the hospital group of stroke-associated deaths surveyed, while in the nursing homes there were seven (46.7 percent) false positives. In reference to definition 2, there were four (8 per-

TABLE 1. — *The Sample of "Stroke Deaths" Used in Study of Evidence Warranting Reporting of Stroke on Death Certificates*

Died at home.....	7	
Single deaths occurring in any given hospital.....	1	
Single deaths occurring in any given nursing home.....	20	
Eligible nursing home death: record not available.....	1	
Total number of cases not studied.....	29	29
Eligible nursing home deaths.....	15	
Eligible hospital deaths.....	50	
Total number of cases studied.....	65	65
Total number of cases.....		94
Total in matched control sample.....	65	
Total studied.....	130	

TABLE 2.—Comparison Between Death Certificates Listing Stroke and Detailed Review of Clinical Record

Result of Clinical review	CASES (Stroke listed on death certificate)						CONTROLS (Stroke not listed on death certificate)					
	Hospital Death		Nursing Home Death		Total		Hospital Death		Nursing Home Death		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stroke by our criteria	46	92.0	7	46.7	53	81.5	11	22.0	3	20.0	14	21.5
Questionable stroke by our criteria	3	6.0	1	6.7	4	6.2	5	10.0	5	33.3	10	15.4
Not stroke by our criteria	1	2.0	7	46.7	8	12.3	34	68.0	7	46.7	41	63.1
TOTALS	50		15		65		50		15		65	

cent) false positives in the hospital group of stroke-associated deaths surveyed, while in the nursing homes there were six (40 percent) false positives.

False negatives were taken as death certificates on which stroke was not listed, yet the medical records contained information which met our criteria for stroke (definition 1), or actually listed stroke as a diagnosis (definition 2). There were 11 (22 percent) false negatives in the hospital group of non-stroke deaths surveyed, and there were three (20 percent) false negatives in the nursing home group by definition 1. In reference to definition 2, there were eight (16 percent) false negatives in the hospital group, and three (20 percent) false negatives in the nursing home group.

Tables 4 and 5 show the proportion of true positives that appears in vital statistics data listing stroke as the underlying cause of death. Combining definitions 1 and 2 to determine the presence of stroke, two definitions for true positives can be formulated. The weaker definition would include any death which either met our criteria for stroke or had stroke listed as such on the clinical record. There were 78 such deaths in our sample, and 35 (44.9 percent) of these had stroke coded as the underlying cause of death (see Table 4). The stronger definition of a true positive would include any death which met our criteria for stroke and had stroke listed as such on the clinical record.

There were 55 such deaths in our study, and 30 (54.5 percent) of these had stroke coded as the underlying cause of death (see Table 5).

Discussion

It should be pointed out that this report is but a pilot study intended to develop a method and it is hoped that publication of this additional effort will stimulate the interest of others in this field. The data were drawn from a single county during a single month, and any generalizations must be guarded.

There was a higher percentage of false positives in the nursing home deaths than in the deaths occurring in hospitals according to both definitions 1 and 2. This was to be expected, since the nursing home records often had little information to justify a diagnosis of stroke and often made no mention of stroke at all. These nursing home records, with their lack of detail, should have the opposite effect in the case of false negatives, which rely on the failure to list stroke on the death certificate and the presence of clinical evidence for a diagnosis of stroke or the actual mention of stroke on the clinical record. However, the percentage of false negatives according to either definition 1 or 2 was about the same for the hospital deaths and the nursing home deaths.

As would be expected, the percentage of cases

TABLE 3.—Comparison Between Death Certificate and Clinical Diagnosis

	CASES (Stroke listed on death certificate)						CONTROLS (Stroke not listed on death certificate)					
	Hospital Death		Nursing home Death		Total		Hospital Death		Nursing home Death		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Stroke diagnosed clinically (stroke listed on the clinical record)	46	92.0	9	60.0	55	84.6	8	16.0	3	20.0	11	16.9
Stroke not diagnosed clinically (stroke not listed on the clinical record)	4	8.0	6	40.0	10	15.4	42	84.0	12	80.0	54	83.1
TOTALS	50		15		65		50		15		65	

TABLE 4.—*Comparison Between Clinical Strokes by the Weaker Definition and Deaths Coded* as Being Due to Stroke—Controls and Cases Combined*

	Stroke coded as underlying cause of death		Stroke not coded as underlying cause of death		Total	
	No.	%	No.	%	No.	%
Stroke diagnosis appearing on chart or meeting our criteria, or both.....	35	44.9	43	55.1	78	100
Stroke diagnosis not mentioned on chart and not meeting our criteria.....	4	7.7	48	92.3	52	100

Of 65 strokes listed on death certificates 39 (60%) were coded as the underlying cause of death.

*The coded cause of death refers to the one coded by Alameda County and is not necessarily the one appearing in the national vital statistics.

in which stroke was coded as the underlying cause of death was higher in association with the stronger definition of true positive than with the weaker definition. The stronger definition would probably include strokes with the most overt symptoms and would exclude more strokes with less clinical justification for the diagnosis. One would anticipate, then, that these more overt and easily diagnosed strokes would be a major factor in the death of the patient, and as such would be more often coded as the underlying cause of death than would the less overt strokes.

It is not possible to say whether the records which were not studied (those of stroke cases in which death occurred at home or cases that were the only stroke death occurring in a given medical institution in the month of April, 1965) were more accurate than the ones which were studied. However, since most of the larger institutions were included in the study, it seems likely that, if anything, the accuracy of death certificates listing stroke has been overestimated in this report.

The percentage of true positive strokes associated with death that eventually are recorded in vital statistics data would be increased if publications of mortality data gave tabulations which took into account secondary underlying and contributory causes of death. Not only would the publication of such tabulations improve estimates of rates, but it would also provide data which would permit

more accurate descriptive analysis of epidemiologic factors in cerebrovascular accidents.

APPENDIX

In all parts of this report, the term stroke is used to refer to all diseases listed under rubrics 330-334 of the International Classification of Diseases 1955 Revision, W.H.O. All other codes for diseases are from the same source.

With any of the criteria listed below, the evidence for stroke was accepted only if the clinical or anatomical lesion was not directly attributable to an infectious process involving the brain or meninges, to a tumor, to a demyelinating disease, or to physical trauma.

Criteria for Stroke:

1) If any of the following were present in the information on the clinical record, the deceased was considered to have had a stroke:

- a) Postmortem evidence to support a diagnosis of stroke
- b) Surgical evidence to support a diagnosis of stroke
- c) Non-traumatic lumbar puncture with bloody cerebrospinal fluid
- d) Angiographic evidence for stroke
- e) Brain stem involvement (functional disturbances attributable to brain stem damage)
- f) Coma

2) If none of the above criteria were mentioned

TABLE 5.—*Comparison Between Clinical Strokes by the Stronger Definition and Deaths Coded* as Being Due to Stroke—Controls and Cases Combined*

	Stroke coded as underlying cause of death		Stroke not coded as underlying cause of death		Total	
	No.	%	No.	%	No.	%
Stroke diagnosis appearing on chart and meeting our criteria.....	30	54.5	25	45.5	55	100
Stroke diagnosis not mentioned on chart or not meeting our criteria, or both.....	9	12.0	66	88.0	75	100

*The coded cause of death refers to the one coded by Alameda County and is not necessarily the one appearing in the national vital statistics.

on the clinical record, but if any of the following chart information was listed, the decedent was considered to have had a questionable stroke:

- a) Nuchal rigidity
- b) Loss of motor function
- c) Deep tendon reflex changes
- d) Pathological reflex and/or clonus

3) If none of the criteria listed in 1) or 2) above appeared in the clinical record, then there was not sufficient evidence to say the decedent had a stroke.

REFERENCES

1. Acheson, R. M.: Mortality from cerebrovascular accidents and hypertension in the Republic of Ireland, *Brit. J. Prev. Soc. Med.*, 14:139-147, July 1960.
2. Acheson, R. M.: Mortality from cerebrovascular disease in the United States, *Public Health Monograph*, 76:23-40, 1966.
3. Borhani, N. O.: Changes and geographical distribution of mortality from cerebrovascular disease, *Amer. J. Public Health*, 55:673-681, May 1965.
4. Goldberg, I. D. and Kurland, L. T.: Mortality in 33 countries from diseases of the nervous system, *World Neurology*, 3:444-465, June 1962.
5. Kannel, W. B., Dawber, T. R., Cohen, M. E., and McNamara, P. M.: Vascular disease of the brain—epidemiologic aspects: the Framingham Study, *Amer. J. Public Health*, 55:1355-1365, Sept. 1965.
6. Moriyama, I. M., Baum, W. S., Haenzel, W. M., and Mattison, B. F.: Inquiry into diagnostic evidence supporting medical certifications of death, *Amer. J. Public Health*, 48:1376-1387, Oct. 1958.
7. President's Commission on Heart Disease, Cancer and Stroke: Report to the President: A national program to conquer heart disease, cancer and stroke, U.S. Government Printing Office, Washington, D.C., vol. 1, Dec. 1964, p. 13.
8. Ross Russel, R. W.: Observations on intracerebral aneurysms, *Brain*, 86:425-442, 1963.
9. Stallones, R. A.: The epidemiology of cerebrovascular disease, *J. Chronic Dis.*, 18:859-872, Aug. 1965.
10. Vital Statistics of the United States: 1963, U.S. Government Printing Office, Washington, D.C., vol. II, part A, 1965, pp. 1-114-1-115.
11. World Health Organization: International classification of diseases: Manual of the international statistical classification of diseases, injuries, and causes of death, World Health Organization, Geneva, vol. 1, 1957.
12. Wylie, C. M.: Cerebrovascular accident deaths in the United States and England and Wales, *J. Chronic Dis.*, 15:85-90, Jan. 1962.
13. Wylie, C. M.: Recent trends in mortality from cerebrovascular accidents in the United States, *J. Chronic Dis.*, 14:213-220, Aug. 1961.
14. Yates, P. O.: A change in the pattern of cerebrovascular disease, *Lancet*, 1:65-69, 11 Jan. 1964.

Interferon—1968

How Much Do We Understand?

MARTIN S. FINKELSTEIN, M.D., AND THOMAS C. MERIGAN, M.D., *Palo Alto*

SINCE ITS DISCOVERY in 1957, interferon has become the subject of intense study throughout the world. Many reviews^{9,40,45,58,75,127,132} are available describing the literature to mid-1967. We are concerned here primarily with recent developments, particularly with regard to some of the still unanswered questions: What is the biological role of interferon? What is the nature of interferon? How and where is it produced? How does interferon act? How long does it persist in the animal? Can a therapeutic use of interferon for the control of human or animal disease be developed?

What is the biological role of interferon?

It has been shown⁵ that the appearance of interferon in the circulation of animals with viral infections coincided with clinical improvement, while measurable antibody appeared days later. Also (as will be discussed below) interferon is active *in vitro* and *in vivo* against experimental virus growth. It appears early in the course of infection, coincident with the increasing viremia and before gross pathologic change can be detected. Interferon has been shown to be present in certain virus infections at the proper time and in adequate quantities to be involved in natural resistance and recovery both at the portal of entry and at the target organ.⁶ From such findings it has generally been thought, and widely publicized, that interferon is a major defense mechanism against infections by viruses to which there has been no previous immunologic contact. Other antiviral mechanisms include fever, leuko-

cytes and lowered pH and hypoxia in infected areas.

The importance of interferon in defense against viral infections has been questioned. Kirn *et al.*⁷⁰ have shown that mice, whose body temperature was raised by placing them in heated rooms, have an increased survival when infected with Vaccinia or Sindbis virus despite a decreased production of interferon. They therefore concluded that hyperthermia was more important for protection than interferon. However, Postic *et al.*⁹⁸ showed that in rabbits there is increased interferon formation at higher body temperatures. Normally, the production of interferon coincides with the pyrexia accompanying virus infections. Other investigators¹⁹ have observed that, although three variants of Mengo virus have decidedly different degrees of pathogenicity, each variant induced comparable amounts of interferon. It was therefore concluded that interferon production *in vivo* is probably not a major factor in protection against Mengo virus.

In human virus infections the presence and titers of interferon do not correlate well with the clinical course. This was true in children with upper respiratory viral infections,¹⁰² where interferon was present in nasal washings and sera early in the course of the infection and at times of fever, but did not relate to the severity of the disease state. Interferon was found in the saliva and sera of persons with mumps infection,¹²⁶ but again, titers of interferon did not seem to be related to clinical severity of the disease. In volunteers undergoing common cold infections produced by rhino- or coxsackie viruses, no interferon was found in the serum,²⁰ but nasal washings contained interferon-like activity. Again, no correlation of interferon

From the Department of Medicine, Division of Infectious Diseases, Stanford University School of Medicine, Palo Alto.

Reprint requests to: Department of Medicine, Division of Infectious Diseases, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304 (Dr. Merigan).

titer with the extent of disease or pattern of virus shedding was observed.

In chronic rubella virus infection of monkey or rat cell tissue cultures,^{30,133} the virus does not destroy the cell monolayer. The rubella virus induces and is itself inhibited by the action of interferon. This results in the development of an equilibrium demonstrated by the presence of low levels of interferon and low levels of virus in the tissue culture fluid. In congenital rubella, no interferon is found in serum or urine of children even during times of active virus shedding.²⁸ Induction of interferon in these children by another virus does not halt the rubella shedding. The role of interferon in rubella infections is not well understood and is at present under study.

On the other hand, it appears that interferon is involved in recovery from certain experimental virus infections. Suppression of interferon titers in mice by metabolic inhibitors results in a higher viremia and increased mortality.¹⁰⁰ Similarly, in herpes simplex¹¹⁹ infections in guinea pigs, trauma causes both an increase of viral growth and dissemination concomitantly with a decrease in interferon production. In experimental vesicular stomatitis virus (vsv) infection of peripheral leukocytes (where the virus replicates primarily in monocytes), interferon protects these cells from the destructive effects of vsv and diminishes vsv production.³⁴

Many oncogenic materials (urethane, x-irradiation, and various hydrocarbons) inhibit interferon formation.²⁶ The oncogenic effects of various aromatic hydrocarbons varies directly with their ability to depress the interferon response. This has led to speculations that the oncogenicity of these agents might be related to their inhibiting effects on endogenous interferon production, allowing latent tumor viruses to express themselves. Obviously the relevancy of these findings to human tumors depends upon the as yet undemonstrated (but likely) role of viruses in the genesis of human tumors.

It has been considered that interferon may act as a regulatory mechanism for protein formation in uninfected cells (perhaps in the regulation of differentiation and development during embryogenesis or regeneration). This suggestion can be evaluated by studying the ability of ribosomes from interferon treated cells to distinguish between various messenger ribonucleic acids (as will be discussed below).

In summary, there is good evidence to suggest that interferon is active in the normal control

of viral infections. Measurement of circulating or secreted interferon may not be an accurate index of the *in situ* cellular protection (analogous to circulating antibody titers in relation to tissue titers). Protection against viruses has been noted even when interferon is no longer present in the circulation. The possible activity of interferon against tumors, or for regulation of host cell metabolism, is, of course, very intriguing, but still highly speculative.

What is the nature of interferon?

The presence of interferons has been demonstrated in vertebrates from fish to man.⁴⁰ Since its discovery, the activity of interferon has been known to depend upon a protein since its activity was destroyed by trypsin digestion, while ribonuclease and desoxyribonuclease had no effect. Characteristically, interferon is non-specific in regard to virus (i. e., effective against a broad range of viruses) but is relatively specific in regard to cell species, (i. e., human interferon protects human cells but not those of mice or chickens). Its antiviral effect is not exerted directly on the virus, but rather is mediated through the host cell. Interferon can be produced readily in tissue culture and in intact animals. Quantitative assay for activity (i. e., protection against subsequent virus infection) is a relatively simple procedure in tissue culture. Interferons have been shown to be acid and heat stable. There is a wide heterogeneity in molecular weights of various interferons produced in tissue culture fluids or appearing in the sera of animals stimulated with different inducing agents. Labeling of interferon with radioactive precursors has not yet been possible. It is thought that each interferon molecule has a very high biological activity (that is, high titers of "purified" interferons have very low protein concentrations). These "purified" preparations, however, are still heavily contaminated with other proteins.

Eleven years after its discovery, the chemical nature of interferon is still unknown. Certainly, a protein is an essential part of the molecule. Some investigators,^{88,92} however, have suggested a carbohydrate moiety also exists in rabbit interferon. These workers have separated a carbohydrate from its protein cofactor and found that it was this carbohydrate moiety that was active *in vivo*. They believe that the protein portion provides the cell species specificity of the molecule. However, as these investigators pointed out, activity of the carbohydrate moiety was lost with trypsin digestion

and the activity *in vitro* could not consistently be restored by mixing the various fractions. Similar work has not been carried out with interferons from other animal species, and it has been questioned whether the rabbit material studied was indeed interferon.

Fantes³⁵ recently studied purified chick interferon employing precise electrophoresis and CM sephadex chromatography. He found a continuum of heterogeneity in the charge and size of interferons. No sugar or polysaccharide moiety was found. Fantes concludes that interferon may be composed of a group of closely related but *not* identical molecules.

Although interferons have been grouped into discrete classes of molecular weights (for example, 20-30,000; 40-60,000; 90-160,000), there does not seem to be any difference in their biologic activities.¹³⁵ Endotoxin and viral-induced rabbit interferons contain both light (46,000 MW) and heavy (100,000 MW) components.^{69,109} The viral induced interferon is predominantly of the lighter type. An early suggestion that this heterogeneity might be related to the nature of the inducer does not therefore seem likely. It also seems unlikely that the heterogeneity of these interferons is related to their cellular origin, since molecules of diverse molecular weights have been found in tissue culture fluids of homogenous cell types.³³

A possible explanation for the diversity of molecular weights of interferons could be the existence of multiple genes, coding for proteins of differing molecular weight but with similar biologic activity. Alternatively, there may be production of a single biologically active molecule which then can combine with any of several proteins of differing molecular weight.

Despite the heterogeneity of molecular weights, there may be similarities in the antigenic determinants of different interferon molecules. Mouse interferons, induced by a variety of agents *in vivo* and *in vitro*, showed similar neutralization curves of their activity by rabbit antibodies to mouse viral induced interferon.^{36,14} This suggests that the biologically active areas of the different molecular weight interferons have the same or similar structure.

The original concept that interferon is strictly species specific has been recently questioned. Monkey interferon has been shown to have species cross reactivity within the monkey genus, and also cross reactivity with human interferon (cross family activity).¹⁷ Mouse interferon showed 5 percent

of its activity was present on hamster cells and 1 percent on rat cells.¹⁵ Desmyter *et al.*²⁷ showed that human interferon made from Newcastle disease virus infected fibroblast cultures, protected rabbit embryo cells, and this has been confirmed by recent studies in our own laboratory. It is clear then that certain interferons have cross species, cross genera, cross family or cross order antiviral activity. Since, as will be described below, interferon acts by inducing the production of a "new" protein in treated cells, species specificity may be due either to an inability of interferons to enter cells of other animal species, or to an inability of the interferon to combine with intracellular receptors in the treated cell.

In summary, at present interferon is an impure heterogenous preparation with definable biological and chemical properties. There are proteins with different molecular weights having these common properties, and are thus termed interferons. Interferons are active against a great range of viruses, but have some cell species specificity.

How is interferon produced?

During the past several years various agents have been shown to induce interferon. These have included living and non-living materials. The living agents have all been intracellular parasites (all major groups of animal viruses, fungal viruses, Trachoma-inclusion conjunctivitis agents, rickettsia, bacteria and protozoa). The non-living materials have been natural (plant phytohemagglutinin, a fungal cell wall carbohydrate and bacterial endotoxin) and synthetic (polyanions including double stranded RNA). There is a wide variability in the interferon inducing capacity of different viruses, and it has been suggested that this capacity may vary inversely with the virulence of a given virus.¹⁰⁴

Among the agents recently found to stimulate interferon have been synthetic anionic plastic copolymers,^{82,83,103} double stranded synthetic ribonucleotide homopolymers,³⁸ and double stranded RNA isolated from Helanine (a fungal virus),⁷⁴ reovirus,¹²² or a bacteriophage.³⁷ These findings have led to speculations that polyanionic molecules may be required for interferon stimulation, and that nucleic acids must be double stranded for interferon stimulation. Other recent studies, however, have shown that neutral nonanionic materials¹³ can also induce interferon.

Adenoviruses have also been shown to induce interferon. Treatment of the virus with trypsin,

however, significantly decreased its interferon stimulating activity, but did not inhibit the ability of the virus to infect the host cell and to replicate.^{10,59} The adenovirus B antigen is lost with trypsin treatment, and the suggestion is made that this protein is required for interferon stimulation. Similarly, heating the adenovirus to 56°C (133°F) (which does not usually affect DNA), destroys its interferon inducing capacity (however its replicative ability was also lost).¹⁰ These findings suggest that factors other than nucleic acids are also involved in the interferon induction process by viruses.

Interferon formation has also been stimulated in normal lymphocytes by phytohemagglutinin, streptolysin O and poke weed mitogen.^{44,128} In addition, interferon production can be noted when lymphocytes from a sensitized individual are exposed to the specific antigen (diphtheria and tetanus toxoids and tuberculin) *in vitro*.⁴⁹ In this connection it is known that higher titers of interferon will be produced *in vitro* to a specific viral inducer in cells taken from animals previously infected with that virus.⁴⁶

An interaction between several cell types is probably not required for interferon production, since interferon can be readily formed by homogeneous fibroblast or epithelial cell monolayers *in vitro*. Interferon induction by viruses *in vivo* has been prevented by treatment with actinomycin D, puromycin or cyclohexamide, while induction by endotoxin has not been affected by these agents.^{60,134} This has led to the concept that preformed interferon exists in cells, and that it is released by some inducers (that is, endotoxin) whereas other inducers stimulate the *de novo* production of interferon. Although the existence of preformed, and stored interferon has been hypothesized, no interferon has as yet been found in unstimulated cells after disruption.

Infection of mice with mouse cytomegalovirus inhibits interferon stimulation by Newcastle disease virus, but not by endotoxin. The basis for this inhibition is not clear since the antibody response to Newcastle disease virus was also suppressed.⁹⁴ Raising the body temperature of rabbits increases production of viral induced interferon, while lowering body temperature decreases its production.⁹⁸ The effect of body temperature on endotoxin induced interferon is minimal. In some studies adrenalectomy did not affect titers of viral induced interferon,^{32,99} but did in others;¹¹¹ increased titers were produced after endotoxin.⁹⁹ Intraven-

ous injection of thorotrast reduces the interferon titer stimulated by viruses, presumably by blocking the reticuloendothelial system (RES); endotoxin induced interferon is less affected.^{23,62} Studies *in vivo* of tolerance (a state of unresponsiveness to a second administration of an inducer) have shown no cross-tolerance between endotoxin and statolon (a fungal virus). Both, however, induce cross-tolerance to virus.¹³⁴ These studies therefore suggest a difference in the mechanisms of interferon production *in vivo* between viruses and endotoxin.

In vitro, interferon has been induced by a variety of viral and non-viral agents. As in the studies *in vivo*, treatment of cell monolayers with inhibitors of RNA and protein synthesis decreases interferon production after virus infection.^{72,108} Interferon production after endotoxin,⁷¹ synthetic double stranded RNA, or polycarboxylate polymers³⁹ was significantly less inhibited. In addition, the kinetics of formation *in vitro* have shown that the latter inducers stimulate early appearance and early peak titers of interferon in comparison with interferon induced by Newcastle disease virus or statolon.^{38,39,171} The existence of what appears to be two separate mechanisms of interferon induction has therefore also been demonstrated *in vitro*.

The stimulus to the cell for interferon production by viruses may not be the original viral RNA which infects the cell, but rather a new RNA formed after infection. If the temperature of cell cultures is raised from 36°C (97°F) to 42°C (108°F), the production of interferon after Semliki virus infection increases, while virus formation decreases.¹⁸ The production of interferon appeared to be correlated with the appearance of a new RNA, which proved on sucrose gradient centrifugation to be a mixture of single and double stranded molecules.¹⁰⁷

Recently, isolated single mouse cells have been studied for interferon production and response to exogenous interferon.⁸⁷ It appears that there is a small percentage of virus infected cells which do not become protected by interferon, even if interferon concentrations are raised considerably. On the other hand, all of these mouse cells can form interferon. Guggenheim *et al.*⁵⁶ studied interferon production after fusing cells of different animal species into a single heterokaryon cell. They fused cells that could with cells that could not produce interferon after virus stimulation; after fusion the normally unresponsive cells were demonstrated to produce interferon. These experiments offer new

approaches to the study of intracellular mechanisms in interferon production. For example, it may be possible to define repressors or other factors modulating interferon release.

Many agents have been found to alter the production *in vivo* of interferon following viral induction. Stress has been shown to increase the growth of herpes simplex virus by decreasing interferon production.¹¹⁹ Corticosteroids, given in amounts well above the usual physiologic range,¹¹¹ decrease interferon production.^{32,39} Agents which block host cell DNA replication (FUDR) or alter its DNA (hydroxylamine) also decrease interferon formation.^{24,106}

The site of interferon production *in vivo* may vary with the inducing agent. Many studies show the reticuloendothelial system (bone marrow, spleen cells, blood leukocytes)^{62,73,115} makes interferon in response to viruses and endotoxin. Sublethal high voltage whole body x-irradiation reduces the interferon response to viral inducers by 90 percent in mice.²⁵ However, the response can be restored by the injection of isologous bone marrow, suggesting the hemopoietic system is the major source of viral induced interferon. Also, as mentioned above, thorotrast blockade of the reticuloendothelial system can decrease the interferon response to viruses and, to a lesser extent, to endotoxin.^{23,62} Mustargen, at doses which reduce the polymorphonuclear leukocyte count by 66 to 75 percent, did not affect the interferon response to viruses or endotoxin, suggesting that this cell type is not critical in interferon formation.⁶² With the carboxylate copolymers, fungal polysaccharides and endotoxin, peritoneal macrophages, and circulating leukocytes seem to be important sites of interferon formation.^{13,39,71} *In vitro*, many cell types can form interferon following viral or polynucleotide inducers, and it is therefore probable that they induce a widespread interferon response *in vivo*, although some cell types may contribute more than others.

In summary, present evidence suggests interferon is a new protein synthesized after viral infection. However, the possibility has been raised that there may exist in cells a preformed interferon which is released by several non-viral inducers.

How does interferon act?

Interferon's effect on cells can be blocked by inhibitors of RNA and protein formation.¹¹⁶ Thus it appears that interferon induces the synthesis of

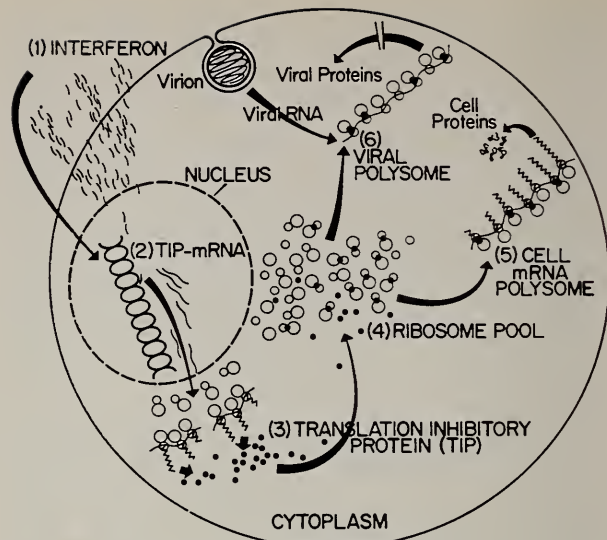


Figure 1.—Model of interferon action. One or a few molecules of interferon (1) act to derepress a host cell cistron, initiate transcription of the messenger RNA, TIP-mRNA (2), which encodes for the translation inhibitory protein (TIP) that in turn is synthesized and accumulates in the cytoplasm (3), where it binds to ribosomes and contributes TIP⁺ units to the ribosome pool (4). Polysomes composed of TIP⁺-ribosomes and cellular mRNA are translated normally (5), whereas, polysomes formed from TIP⁺-ribosomes and viral RNA are not translated (6)—producing a state of interferon-mediated interference. (Reproduced from *Virology*, 30:3, Nov. 1966, p. 514, with permission from Academic Press, Inc.)

another protein ("antiviral protein") within the treated cells, and it is this second protein which protects against virus infections. This second protein interrupts the synthesis of viral protein at the ribosomal level. The infected cell, protected by interferon, may still be destroyed (depending upon the nature of the infecting virus), but virus replication is aborted and other cells are thus saved from virus infection. Marcus and Salb⁸⁰ have suggested that a new protein appears on ribosomes of interferon treated cells. Figure 1 shows the model of interferon activity they proposed. Infecting virus enters cells and releases messenger RNA, but translation of this messenger RNA into viral proteins is blocked. This effect on the ribosomes does not, however, affect their ability to recognize and translate host cell RNA.

There have been several materials described which inhibit the activity of interferon. "Stimulon" and "enhancer" are both virus induced proteins that inhibit the action of interferon and thereby enhance virus replication.^{21,68} A third substance, "blocker," has been recognized which inhibits production, but not the action, of interferon.⁶³ This material is not sensitive to proteolytic enzymes. A protein isolated from crude L cell interferon

(produced in response to Newcastle disease virus infection) inhibits the action of interferon against Mengo virus in Mouse Ehrlich Ascites cells but not in mouse L cells.¹²¹ In addition, it has been shown that 40 percent fetal calf serum or 5 to 10 percent dimethyl-sulfoxide (DMSO) can inhibit the activity of interferon.¹²⁴ Too little is known about these materials to permit an explanation of the mechanism of their activity, or their interrelationship.

There are several materials which potentiate the action of interferon. One such is coferon, a protein extract from *E. coli*, active *in vitro*,¹²⁵ another is poly L-ornithine.¹¹⁷ In the latter case, the mechanism is better understood; namely, it is the polycationic nature of poly L-ornithine which allows greater penetration of interferon into treated cells.

Interferon is active against a broad range of viruses, although there is variation in the sensitivity of viruses to interferon. Adenoviruses⁹⁵ and cytomegalovirus⁹³ are among the more resistant virus types. It is possible that the messenger RNAs of these viruses are similar to those of the cell and therefore are translated by the ribosomes in the interferon treated cell. Interferon is also active in protecting cells against agents of the trachoma conjunctivitis group⁵⁷ which are more like bacteria than viruses in their replicative cycle, and also have their own ribosomes.

Recent collaborative studies between Dr. J. S. Remington and ourselves demonstrated the replication of a protozoan (*Toxoplasma gondii*) in tissue culture to be inhibited by highly purified interferon. In addition, interferon inducing agents have been found to be active against *P. Berghei malariae* in the mouse by Drs. Jahiel, Vilcek, Nussensweig and Vanderberg. Both these soon to be published observations suggest the need for examining the interferon mechanism in a wide variety of intracellular parasitic states.

Baron *et al.*,⁷ studying the requirements for interferon mediated protection of mouse embryo cells, showed that if interferon was removed from the culture fluid, the antiviral protection persisted unchanged for 28 hours, and then declined. Increase in protection, however, was seen within seven hours after the addition of more interferon. Maintenance of protection required continued cellular RNA and protein synthesis. If new RNA or protein synthesis was blocked, the antiviral protection persisted for only seven to sixteen hours. It has been shown that a portion of interferon may become fixed to the cell, and for several hours con-

tinues to stimulate the "antiviral protein" even after the cells have been washed free of interferon.^{76,79} Interferon can become fixed to chick cells in the cold but does not stimulate the "antiviral protein" until the cells are warmed to 37°C (98.6°F).^{43,124} The interferon could not be washed off, but was removed by trypsin.

The effect of interferon on DNA viruses is not an all-or-none effect (for review see reference 31). This was demonstrated by Joklik and Merigan, who have studied the effect of interferon on vaccinia virus infection of L cells.⁶⁴ Interferon caused a decrease of DNA polymerase and viral DNA at concentrations much higher than required to inhibit whole virus production.⁷⁷ This is not surprising since production of mature virions requires many enzymes, each one inhibited in formation by interferon. Interferon also inhibits the production of an alkaline DNase which appears after vaccinia infection, but again at concentrations much higher than those required to inhibit virus production.¹²

In RNA virus (Mengo virus) infection of L cells, interferon prevents the appearance of the replicative double stranded form of RNA.⁴⁸ The amount of RNA polymerase produced by RNA viruses is also decreased; the specific activity of this enzyme is not affected.^{86,113} Again, production of mature virus is more inhibited than the RNA polymerase.

Interferon action on oncogenic viruses has been studied in several laboratories. In newborn hamsters interferon inhibited tumor formation by polyoma virus,² and in chick cells by Rous sarcoma virus.⁴ The ability of SV 40 to transform monkey and human cells was decidedly inhibited. Much less inhibition was noted on transformation by adenoviruses.⁹⁵ SV 40 virus T antigen can only be inhibited during the first generation cycle of the cells; thereafter, T antigen development becomes insensitive to interferon inhibition, suggesting that the DNA coding for this antigen had become part of the host cell DNA.¹¹⁸

Ribosomes isolated from interferon treated cells have been found to contain proteins which are not present on the ribosomes of untreated cells.^{78,89,105} Ribosomes from interferon treated cells can distinguish between host cell and viral RNA, and this selective ability can be removed by trypsin.¹⁰⁵

In summary, interferon appears to stimulate cells to form another protein which is thought to combine with ribosomes and, by so doing, confer upon them the ability to selectively accept host cell messenger RNA, and reject "foreign" messengers.

How long does interferon persist in the animal?

Little is known about the fate of interferon within the cell or the animal. Some studies have shown that interferon is taken up by cells in tissue culture, whereas other studies have not. Baron and Buckler¹⁶ demonstrated that there is no loss of mouse serum interferon activity when it was incubated on mouse embryo cells. Consistent with this finding was the observation that concentration, rather than total amount of interferon was the factor determining degree of viral protection.¹⁶ Others have shown that interferon produced in tissue cultures loses activity during incubation with cell monolayers which are being protected.¹²⁰ Differences in purity of interferon may account for some of the discrepant results since this laboratory has shown that purified interferons are less stable than crude.⁸⁵

In vivo, interferon has been found in the urine of animals given exogenous interferon, or in which endogenous interferon was actively produced. Ho and Postic⁶¹ calculated a renal clearance of 30.6 ml in one hour for viral and 1.2 ml an hour for endotoxin induced interferon. Reasons for this difference probably relate to the lower molecular weight of the virus-induced interferon compared with the endotoxin interferon. Study of the molecular weight of urine interferons has revealed them to be of rather homogenous low molecular weight, despite heterogenous molecular weight serum interferons. In the serum of the mouse or rabbit, viral interferon has a half life of approximately 11 minutes. Whether this is due to interferon absorption onto cells or to degradation is not known, but the amounts eliminated in urine do not account for its rapid loss. After injection of interferon into pregnant rabbits, there is an apparent uptake by the liver and spleen, so that after 30 minutes the liver and spleen have approximately ten-fold more interferon than the serum on a weight basis. No interferon was detected in the foetus. Injection of Sindbis virus into pregnant rabbits resulted in a high titer of interferon in the maternal spleen and placenta in contrast to low titers in the liver and kidney. In this case, in contrast to the previous study utilizing passive administration of interferon, interferon was found in the foetal blood.⁶²

Other studies have shown that systemically induced interferon can be transported through membranes. In isolated gut perfusion experiments, interferon has been shown to be excreted into the

bowel,¹¹ and has been found in the aqueous humor and cerebrospinal fluid of rabbits injected with endotoxin.⁹⁰ Interferon has also been found in cerebrospinal fluid of humans in whom interferon was induced by the intravenous injection of Newcastle disease virus.²²

In summary, interferon activity is rapidly lost from the circulation of an animal given interferon passively. The fate of interferon molecules is still not known, since only biological activity can be measured. Interferon activity can cross biological membranes, and thus systemically developed interferon has been found in the cerebrospinal fluid, urine, aqueous humor, foetal blood and gut lumen.

What is the therapeutic potential of interferon?

The practical application of interferon has been under consideration since it was first discovered. There is obvious need for effective antiviral agents for treatment both of man and domestic animals, particularly against the common viral infections in which the number of different serotypes precludes effective immunization. Interferon is already being used as a laboratory tool in the study of protein synthesis and the mechanisms of virus replication, and as a diagnostic tool in discovering latent cellular virus infections. The use of interferon in human and animal disease has presented several problems. Interferon is fairly species-specific, so that for human disease, human or primate interferon must be used. The production of human interferon requires readily available human tissue. Human amnion,⁴² peripheral leukocytes,^{50,114,129} and cultured fibroblasts⁸⁴ all can make high titers of interferon and provide a large potential source of human interferon. However, interferon is very short lived in the circulation, and for effective therapy relatively large quantities of high titered interferon would be required.

Many types of interferon inducers have been shown to protect animal hosts from viral infections. Utilizing this technique thus seems to be a fruitful approach to the therapeutic use of interferon; but the problems of immunogenicity and toxicity of interferon inducers, as well as the dangers inherent in long-term interferon induction, must be carefully studied.

-In the USSR, interferon, or virus inducers of interferon, are claimed to have been successfully used in clinical trials in experimentally induced influenza,¹¹² herpetic skin lesions,¹⁰¹ viral dermatosis,¹ and the eye lesions^{3,66,67} caused by herpes

simplex, adenovirus, and trachoma. Influenza was reduced by 80 percent in treated volunteers. In herpes zoster or herpes simplex infection, 50 percent of the patients showed significant clinical improvement while in other skin infections (warts, condylomata acuminatum, molluscum contagiosum) there was no benefit. Superficial herpetic lesions of the eye were improved in six of ten patients given local drops or ointments containing interferon. Interferon was also effective prophylactically and as therapy for adenovirus conjunctivitis. In patients with trachoma (stages I, II, and III), local and subcutaneous injections of interferon were as effective as antibiotic therapy with sulfonamides; however, no side effects such as allergic reactions to the interferon developed.

Experimental animal studies serve as useful models for measuring the protective effects of interferon (for review see references 5 and 40). However, the virus infecting dose may not correlate well with those of naturally occurring virus infections. Oh and Gill⁹¹ have shown that intravenous administration of bacterial endotoxin protects rabbit corneas against the toxic effects of Newcastle disease virus, presumably by interferon stimulation since interferon was found in the aqueous fluid. Finter⁴¹ gave mice interferon and then challenged them with doses of Semliki Forest virus which should kill approximately 50 percent of the control animals. Interferon, at doses of 250 units or greater, given intramuscularly or intravenously one day before virus challenge, reduced the lethality of the virus. Interferon at doses of 5000 units, given four to five days before, or 18 hours after intracerebral virus challenge, also protected the mice. In addition, infants given live measles vaccine to induce interferon formation, are protected against vaccinia challenge.⁹⁷

Interferon can also be used in etiologic investigations of disease. Adjuvant induced arthritis in rats has been successfully treated with statolon.⁶⁵ The suggestion has been made, therefore, that this disease is mediated by an infectious agent sensitive to interferon.

In addition, interferon induction may be an important consideration in the commercial preparation of virus strains. A live attenuated rubella vaccine was selected because of its high interferon inducing capacity.⁹⁶

Clinical use of interferon for the control of viral infection requires careful evaluation of the mode of virus dissemination and of the production of disease. Rabies virus infection in mice was not

affected by high titers of statolon induced interferon.^{8,110} This failure to protect may be because the virus is located in areas where insufficient interferon titers could be attained (that is, in the nerve roots and within brain cells). Part of the success of Oh⁹¹ in preventing Newcastle disease virus corneal infections of rabbits by endotoxin was in reducing the permeability of the aqueous fluid to interferon by a secondary effect of endotoxin. Another problem is the possibility of inhibiting the immune response to the infecting virus by limiting the infection at too early a stage.²⁹ Interferon itself, however, does not inhibit the immune response.⁸¹

In the treatment of virus induced tumors it has already been mentioned that interferon can inhibit SV 40, oncogenic adenoviruses, Rous sarcoma virus, and polyoma virus.^{2,4,95,118} Injection of interferon did not protect mice against Rauscher virus leukemia in one study¹²³ but did in others.^{47,51} The leukemia induced by Friend virus can be inhibited by interferon, statolon or Sendai virus, even when these are given after the disease has begun.^{52,53,54,55,130,131}

The search for a safe, clinically useful interferon inducer has led to the demonstration that synthetic plastics and double stranded RNAs can induce interferon.^{38,83} These agents do not have the drawbacks of virus inducers—namely, immunogenicity and potentially latent untoward effects because of viability of the inducer. Both of these agents have already been successfully used in virus protection studies in mice.⁸³ Both materials have been found to be minimally toxic, and the polycarboxylate protects animals for periods of months following a single administration of the material. However, the synthetic polycarboxylate is less active on a weight basis, is poorly eliminated and accumulates in the reticuloendothelial system. The hazard of having such a material remain in the animal for a long period is unknown, but it would seem to be desirable that the inducing agent be degraded more rapidly. The synthetic double stranded RNA is eliminated more readily, but protection from virus infection appears to be much more transient. Perhaps organic chemists can create other synthetic agents intermediate in their degradability and in their duration of activity.

In summary, interferon has already been successfully used in the protection of humans and experimental animals against viral diseases, including virulent and oncogenic viruses. For practical purposes, inducers of interferon, rather than

interferon itself, may be the best method of administering interferon to individuals.

REFERENCES

- Ashmarin, Y., Vilner, L., Zeidenok, N., Shatova, L., Amitan, B., Vedrovich, T., and Komlev, V.: The experience of interferonogen IVS application for treating viral and other dermatosis. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 69-73 (Rus).
- Atanasiu, P., and Chany, C.: Action d'un interferon provenant de cellules malignes sur l'infection experimentale du hamster nouveau-ne par le virus du polyome. *Compt. Rend. Acad. Sci.*, 251:1687-1689, 17 Oct. 1960.
- Babushkin, V.: The first experience of interferonogen application in the treatment of trachoma. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 102-107 (Rus).
- Bader, John: Production of interferon by chick embryo cells exposed to Rous sarcoma virus. *Virology*, 16:436-443, Apr. 1962.
- Baron, Samuel: The biological significance of the interferon system. *From Interferons*, edited by E. B. Finter, W. B. Saunders Company, Philadelphia, 1966, pp. 268-293.
- Baron, S.: Host defenses during virus infection, *from Modern Trends in Medical Virology*, edited by R. B. Heath and B. P. Waterson, Butterworths, London, 1967.
- Baron, S., Buckler, C. E., Levy, H. B., and Friedman, R. M.: Some factors affecting the interferon-induced antiviral state. *Proc. Soc. Exp. Biol. and Med.*, 125:1320-1326, Aug. 1967.
- Baron, S., and Habel, K.: Personal communication, 1968.
- Baron, S., and Levy, H.: Interferon. *Ann. Rev. of Microbiol.*, 20:291-318, 1966.
- Beladi, I., and Pusztai, R.: Interferon-like substance produced in chick fibroblast cells inoculated with human adenoviruses. *Z. Naturforsch.*, 22:165-169, 1967.
- Bocci, V., Russi-Sorce, M., Cirri, G., Rita, G., and Cantagalli, P.: Virus-induced interferon in the rabbit: distribution, fate and characterization of urinary interferons. *From International Symposium on Interferon*, edited by G. Rita, in press, 1968.
- Bodo, G., and Jungwirth, C.: Effect of interferon on deoxyribonuclease induction in chick fibroblast cultures infected with Cowpox virus. *J. Virol.*, 1(3):446-471, June 1967.
- Borecky, L., Lackovic, V., Blaskovic, D., Masler, L., and Sikl, D.: An interferon-like substance induced by mannans. *Acta Virol.*, II, 264-266, May 1967.
- Boxaca, M., and Paucker, K.: Neutralization of different murine interferons by antibody. *J. Immunol.*, 98(6):1130-1135, June 1967.
- Buckler, C. E., and Baron, S.: Antiviral action of mouse interferon in heterologous cells. *J. Bacteriol.*, 91(1):231-235, Jan. 1966.
- Buckler, C. E., Baron, S., and Levy, H.: Interferon: lack of detectable uptake by cells. *Science*, 152:80-82, 1 Apr. 1966.
- Bucknall, Robert A.: "Species specificity" of interferons: a misnomer? *Nature*, 216(5119):1022-1023, 9 Dec. 1967.
- Burke, D. C., Skehel, J. J., and Low, M.: Interferon production and viral ribonucleic acid synthesis in chick embryo cells. *J. Gen. Virol.*, 1:235-237, Apr. 1967.
- Campbell, J. B., and Colter, J. S.: Sensitivity to, and production of interferon by three variants of Mengo virus. *Canad. J. Microbiol.*, 13:931-937, Aug. 1967.
- Cate, T. R., Douglas, R. G., Jr., and Couch, R. B.: Interferon and the common cold. *Clin. Res.*, 16:84, Jan. 1968.
- Chany, C., and Brailovsky, C.: Les stimulons, facteurs antagonistes de l'interferon favorisant la multiplication intracellulaire des virus. *Compt. Rend. Acad. Sci.*, 261:4282-4285, 15 Nov. 1965.
- Clever, L., Waddell, D., and Merigan, T.: Personal communication, 1968.
- Considine, R. G., and Starr, T. J.: Role of the reticuloendothelial system in interferon tolerance. *J. Reticuloendothelial Soc.*, 4: 315-325, Nov. 1967.
- Caro, V., Galeota, C. A., and Coraggio, F.: Inhibition of interferon production by a halogenated pyrimidine derivative: 5-fluoro-2'-deoxyuridine. *Texas Rep. on Biol. and Med.*, 24:158-163, Summer, 1966.
- DeMaeyer, E., Jullien, P., and DeMaeyer-Guignard, J.: Personal communication, Feb. 1968.
- DeMaeyer, E., and DeMaeyer-Guignard, J.: Effect of different carcinogenic agents on the production of interferon in tissue culture and the animal. *From Interferon*, Ciba Found. Symp., edited by G. E. Wolstenholme and M. O'Connor, J. and A. Churchill, Ltd., London, 1968, pp. 218-235.
- Desmyter, J., Rawls, W. E., and Melnick, J. L.: A human interferon that crosses the species line. *Proc. Natl. Acad. Sci.*, 59:69-76, Jan. 1968.
- Desmyter, J., Rawls, W. E., Melnick, J. L., Yow, M. D., and Barrett, F. F.: Interferon in congenital rubella: response to live attenuated measles vaccine. *J. Immunol.*, 99(4):771-777, Oct. 1967.
- DeSomer, P., Billiau, A., DeClercq, E.: Inhibition of antibody production in rats and mice by intravenous injection of interferon-inducing amounts of Sindbis virus or E. Coli. *Arch. Ges. Virusforsch.*, 20(2):205-214, Mar. 1967.
- DeSomer, P., Billiau, A., DeClercq, E., and Schonne, E.: Rubella virus interference and interferon production. *Antonie van Leeuwenhoek*, 33(3):237-245, 1967.
- DeSomer, P., and Cocito, C.: The mode of action of interferon. *From Interferon*, Ciba Found. Symp., edited by G. E. Wolstenholme and M. O'Connor, J. and A. Churchill, Ltd., London, 1968, pp. 128-140.
- DeSomer, P., DeClercq, E., and Billiau, A.: Influence of whole-body irradiation, cortisol treatment and adrenalectomy on interferon induction *in vivo* in rats. *From Medical and Applied Virology*, edited by M. Sanders and E. Lannette, W. A. Green, Inc., St. Louis, Mo., 1968, pp. 230-243.
- Duc-gorian, P., Falcoff, E., and Chany, C.: Personal communication, 1967.
- Edelman, R., and Wheelock, E. F.: Specific role of each human leukocyte type in viral infections. I. Monocyte as host cell for vesicular stomatitis virus replication *in vitro*. *J. Virol.*, 1(6):1139-1149, Dec. 1967.
- Fantes, Karl: Purification and physico-chemical properties of interferons. *From International Symposium on Interferon*, edited by G. Rita, Academic Press, in press, 1968.
- Fauconnier, B.: Antigenic identity of interferons induced by different viruses in the same cell system. *Nature*, 214(5088):591, 6 May 1967.
- Field, A. K., Lampson, G. P., Tytell, A. A., Nemes, M. M., and Hilleman, M. R.: Inducers of interferon and host resistance. IV. Double-stranded replicative form RNA (MS2-RF-RNA) from E. Coli infected with MS2 coliphage. *Proc. Nat. Acad. Sci.*, 58:2102-2108, Nov. 1967.
- Field, A. K., Tytell, A. A., Lampson, G. P., and Hilleman, M. R.: Inducers of interferon and host resistance. II. Multistranded synthetic polynucleotide complexes. *Proc. Nat. Acad. Sci.*, 58:1004-1010, Sep. 1967.
- Finkelstein, M. S., Bausek, G. H., and Merigan, T. C.: Interferon induction *in vitro*: inducer dependent difference in sensitivity to inhibitors of RNA and protein synthesis, in press, 1968.
- Finter, Norman: Interferon. W. B. Saunders Company, Philadelphia, 1966.
- Finter, Norman: Interferon in mice protection against small doses of virus. *J. Gen. Virol.*, 1:395-397, July 1967.
- Fournier, F., Falcoff, E., Chany, C.: Demonstration, mass production and characterization of a heavy molecular weight human interferon. *J. Immunol.*, 99(5):1036-1041, Nov. 1967.
- Friedman, Robert M.: Interferon binding: the first step in establishment of antiviral activity. *Science*, 156(3783):1760-1761, 30 June 1967.
- Friedman, R. M., and Cooper, H. L.: Stimulation of interferon production in human lymphocytes by mitogens. *Proc. Soc. Exp. Biol. Med.*, 125:901-905, July 1967.
- Glasgow, Lowell A.: Interferon: a review. *J. Ped.*, 67:104-121, July 1965.
- Glasgow, Lowell A.: Leukocytes and interferon in the host response to viral infections. II. Enhanced interferon response of leukocytes from immune animals. *J. Bact.*, 91:2185-2191, June 1966.
- Glasgow, Lowell A.: Personal communication, 1967.
- Gordon, I., Chenault, S., Stevenson, D., and Acton, J.: Effect of interferon on polymerization of single-stranded and double-stranded Mengo-virus ribonucleic acid. *J. Bact.*, 91:1230-1238, Mar. 1966.
- Green, J. A., and Kibrick, S.: Immune stimulation of interferon production in human blood lymphocyte cultures. *Fed. Proc.*, 27(2): 561, Apr. 1968.
- Gresser, I.: Production of interferon by suspensions of human leukocytes. *Proc. Soc. Exp. Biol. Med.*, 108:799-803, Dec. 1961.
- Gresser, I., Coppey, J., Fontaine-Brouy-Boye, D., Falcoff, E., Falcoff, R., Zajdela, F., Bourali, C., and Thomas, M. T.: The effect of interferon preparations on Friend leukemia in mice. *From Interferon*, Ciba Found. Symp., edited by G. E. Wolstenholme and M. O'Connor, J. and A. Churchill, Ltd., London, 1968, pp. 240-248.
- Gresser, I., Coppey, J., Falcoff, E., and Fontaine, D.: Action inhibitrice de l'interferon brut sur le developement de la leucemie de Friend chez la souris. *Comp. Rend. Acad. Sci.*, 263:586-588, Series D, 1 Aug. 1966.
- Gresser, I., Coppey, J., Falcoff, E., and Fontaine, D.: Interferon and murine leukemia I. Inhibitory effect of interferon preparations on development of Friend leukemia in mice. *Proc. Soc. Exp. Biol. and Med.*, 124:84-91, Jan. 1967.
- Gresser, I., Coppey, J., Fontaine-Brouy-Boye, D., and Falcoff, R.: Interferon and murine leukemia. III. Efficacy of interferon preparations administered after inoculation of Friend virus. *Nature*, 215: 174-175, 8 July 1967.
- Gresser, I., Falcoff, R., Fontaine-Brouy-Boye, D., Zajdela, F., Coppey, J., and Falcoff, E.: Interferon and murine leukemia. IV. Further studies on the efficacy of interferon preparations administered after inoculation of Friend virus. *Proc. Soc. Exp. Biol. Med.*, 126: 791-796, Dec. 1967.
- Guggenheim, M. A., Friedman, R. M., and Rabson, A. S.: Interferon production by chick erythrocytes activated by cell fusion. *Science* 159:542-543, 8 Dec. 1967.
- Hanna, L., Merigan, T., and Jawetz, E.: Inhibition of TRIC agents by virus-induced interferon. *Proc. Soc. Exp. Biol. Med.*, 122: 417-421, June 1966.
- Hilleman, Maurice R.: Immunologic, chemotherapeutic and interferon approaches to control of viral disease. *Am. J. Med.*, 38: 751-766, May 1965.
- Ho, M., and Kohler, K.: Personal communication, Feb. 1967.
- Ho, M., and Kono, Y.: Effect of Actinomycin D on virus and

- endotoxin induced interferon-like inhibitors in rabbits, *Proc. Nat. Acad. Sci.*, 53:220-224, Jan. 1965.
61. Ho, M., and Postic, B.: Renal excretion of interferon, *Nature*, 214:1230-1231, 17 June 1967.
62. Ho, M., Postic, B., and Ke, Y.: The systemic induction of interferon. *From Ciba Found. Symp.*, edited by G. E. Wolstenholme and M. O'Connor, J. and A. Churchill, Ltd., London, 1968, pp. 19-35.
63. Isaacs, A., Rotem, Z., and Fantes, K. H.: An inhibitor of the production of interferon ("blocker"), *Virology*, 29:248-254, May 1966.
64. Joklik, W. K., and Merigan, T. C.: Concerning the mechanism of action of interferon, *Proc. Nat. Acad. Sci.*, 56:558-565, Aug. 1966.
65. Kapusta, M. A., and Mendelson, J.: Inhibition of adjuvant arthritis by statolon, *Proc. Soc. Exp. Biol. Med.*, 126:496-499, 29 June 1967.
66. Kasparov, A., Kunicheva, G., Kalikova, L., Vilner, L., and Zeidenok, N.: Interferon IVS in the treatment and prophylaxis of adenovirus induced lesions of the eye. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 85-94, (Rus.).
67. Kasparov, A., Vilner, L., and Zeidenok, N.: Treatment of herpetic lesions of eyes with interferonogens IVS. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 75-83 (Rus.).
68. Kato, N., Ohta, F., and Okada, A.: Counteraction between interferon and enhancer, *Virology*, 28:785-788, Apr. 1966.
69. Ke, Y. H., Merigan, T. C., and Ho, M.: Heterogeneity of rabbit serum interferons, *Nature*, 211:541-542, 30 July 1966.
70. Kirn, A., Schieffer, A., Tinland, R.: Lack of correlation between production of interferon and protection of temperature in mice infected with Sindbis virus, *Nature*, 215(5096):86-87, 1 July 1967.
71. Kono, Yuji, Interferon-like inhibitor produced in bovine leukocyte cultures after inoculation with endotoxin, *Arch. Ges. Virusforsch.*, 21(2):276-281, Sep. 1967.
72. Kono, Yuji: Rapid production of interferon in bovine leukocyte cultures, *Proc. Soc. Exp. Biol. Med.*, 124:155-160, Jan. 1967.
73. Kono, Y., and Ho, M.: The role of the reticuloendothelial system in interferon formation in the rabbit, *Virology*, 25:162-166, Jan. 1965.
74. Lampson, G. P., Tytell, A. A., Field, A. K., Nemes, M. M., and Hilleman, M. R.: Inducers of interferon and host resistance. I. Double stranded RNA from extracts of penicillium funiculosum, *Proc. Nat. Acad. Sci.*, 58(2):782-789, Aug. 1967.
75. Larke, R. P. Bryce: Interferon: a changing picture, *Canad. Med. Ass. J.*, 94:23-31, 1 Jan. 1966.
76. Levine, S.: Persistence of active interferon in cells washed after treatment with interferon, *Proc. Soc. Exp. Biol. Med.*, 121:1041-1045, Apr. 1966.
77. Levine, S., Magee, W. E., Hamilton, R. D., and Miller, O. V.: Effect of interferon on early enzyme and viral DNA synthesis in vaccinia virus infection, *Virology*, 32(1):33-40, May 1967.
78. Levy, H. B., Carter, W.: Buckler, C., Snellbaker, R., and Baron, S.: Action and induction of interferon, *Bact. Proc. V63* (Abst.), May 1966.
79. Lockart, Royce Z., Jr.: Analysis of additional interference occurring after the removal of interferon, *J. Virol.*, 1(6):1158-1163, Dec. 1967.
80. Marcus, P. I., and Salb, J. M.: Molecular basis of interferon action: inhibition of viral RNA translation, *Virology*, 30:502-516, Nov. 1966.
81. Mazzur, S. R., and Paucker, K.: Studies on the effect of interferon on the formation of antibody in mouse spleen cells. II. The effect of interferon on antibody plaque formation and antibody production by transferred spleen cells, *J. Immunol.*, 98(4):689-696, Apr. 1967.
82. Merigan, Thomas C.: Induction of circulating interferon by synthetic anionic polymer of known composition, *Nature*, 214:416-417, 22 Apr. 1967.
83. Merigan, T. C., and Finkelstein, M. S.: Interferon stimulating and *in vivo* antiviral effects of various synthetic anionic polymers, *Virology*, in press, 1968.
84. Merigan, T. C., Gregory, D., and Petralli, J.: Physical properties of human interferon *in vivo* and *in vitro*, *Virology*, 29:515, Aug. 1966.
85. Merigan, T. C., Winger, C. A., and Dixon, C. B.: Purification and characterization of vertebrate interferons, *J. Mol. Biol.*, 13:679-691, Oct. 1965.
86. Miner, N., Ray, W. J., Jr., and Simon, E. H.: Effect of interferon on the production and action of viral RNA polymerase, *Biochem. and Biophys. Res. Comm.*, 24:264-268, 20 July 1966.
87. Miner, N. A., and Simon, E. H.: Interferon production by single cells, *Bact. Proc.*, in press, 1968.
88. Nagano, Y.: Studies on virus inhibiting factor, *Jap. J. Exp. Med.*, 37(2):183-187, 1967.
89. Ng, M. H., Vilecek, J., and Merigan, T. C.: Effect of interferon on the synthesis of ribosomal proteins in chick embryo cells, *Bact. Proc.*, in press, 1968.
90. Oh, Jang O.: An interferon-like viral inhibitor in body fluids of endotoxin-injected rabbits, *Proc. Soc. Exp. Biol. and Med.*, 123:493-496, Nov. 1966.
91. Oh, J. O., and Gill, F. J.: Role of interferon-like viral inhibitor in endotoxin-induced corneal resistance to Newcastle Disease Virus, *J. Bact.*, 91:251-256, Jan. 1966.
92. Okazaki, H.: Purification and properties of an inhibitory factor of virus replication, *Jap. J. Exp. Med.*, 37(2):159-168, 1967.
93. Osborn, J. E., and Medearis, D. N., Jr.: Studies of relationship between mouse cytomegalovirus and interferon, *Proc. Soc. Exp. Biol. Med.*, 121:819-824, Mar., 1966.
94. Osborn, J. E., and Medearis, D. N., Jr.: Suppression of interferon and antibody and multiplication of Newcastle disease virus in cytomegalovirus infected mice, *Proc. Soc. Exp. Biol. Med.*, 124:347-353, Feb. 1967.
95. Oxman, M. N., Rowe, W. P., and Black, P. H.: Studies of adenovirus SV 40 hybrid viruses. VI. Differential effects of interferon on SV 40 and adenovirus T antigen formation in cells infected with SV 40 virus, adenoviruses and adenoviruses-SV 40 hybrid viruses, *Proc. Natl. Acad. Sci.*, 57(4):940-948, Apr. 1967.
96. Parkman, P. D., Meyer, H. M., Jr., Kirchstein, R. L., and Hopps, H. E.: Attenuated rubella virus. I. Development and laboratory characterization, *New Eng. J. Med.*, 275:569-574, 15 Sep. 1966.
97. Petralli, J. K., Merigan, T. C., and Wilbur, J.: The action of endogenous interferon against vaccinia infection in children, *Lancet* ii, 401-405, 28 Aug. 1965.
98. Postic, B., DeAngelis, C., Breinig, M., and Ho, M.: Effect of temperature on the induction of interferons by endotoxin and virus, *J. Bact.*, 91:1277-1281, Mar. 1966.
99. Postic, B., DeAngelis, C., Breinig, M. K., and Ho, M.: Effect of cortisol and adrenalectomy on induction of interferon by endotoxin, *Proc. Soc. Exp. Biol. Med.*, 125:89-92, May 1967.
100. Postic, B., Singer, S., and Ho, M.: Determinants of pathogenicity of Sindbis virus for adult mice, *Fed. Proc.*, 23:193, 1964.
101. Rahmnanov, V., Porekayev, N., Konstantinov, A., Samgin, M., and Vilner, L.: Interferon IVS and IVBN in the therapy of skin herpetic lesions. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 63-68 (Rus.).
102. Ray, G. C., Gravelle, C. R., and Chin, T. D. Y.: Circulating interferon in infants and children with acute respiratory illness, *J. Ped.*, 71(1):27-32, July 1967.
103. Regelson, William: Prevention and treatment of Friend leukemia virus infection by interferon inducing synthetic polymers, *Proc. Int. Symp. on Atherosclerosis and Reticuloendothelial Systems*, in press, 1967.
104. Ruiz-Gomez, J., and Isaacs, A.: Optimal temperature for growth and sensitivity to interferon among different viruses, *Virology*, 19:1-7, Jan. 1963.
105. Salb, J., and Marcus, P.: Personal communication, 1968.
106. Skehel, J. J., and Burke, D. C.: Virus nucleic acid and interferon formation, *Biochem. J.*, 103:71, Apr. 1967.
107. Skehel, J. J., and Burke, D. C.: Personal communication, 28 Feb. 1968.
108. Smith, T. J., and Wagner, R. R.: Rabbit macrophage interferons. I. Conditions for biosynthesis by virus-infected and uninfected cells, *J. Exp. Med.*, 125:559-577, Apr. 1967.
109. Smith, T. J., and Wagner, R. R.: Rabbit macrophage interferons. II. Some physicochemical properties and estimation of molecular weights, *J. Exp. Med.*, 125:579-593, Apr. 1967.
110. Soave, Orland, A.: Influence of statolon-induced interferon on rabies virus infection in mice, *Am. J. of Vet. Research*, in press, 1968.
111. Solomon, G. F., Merigan, T. C., and Levine, S.: Variation in adrenal cortical hormones with physiologic ranges, stress and interferon production in mice, *Proc. Soc. Exp. Biol. and Med.*, 126:74-79, Oct. 1967.
112. Solovjov, V., Bektemirov, L., Porubel, L., and Churkin, G.: Prophylactic effect of inducers of endogenous interferon in experimental influenza. *From Interferons and Interferonogens*, Institute of Poliomyelitis and Viral Encephalitis, Moscow, 1967, pp. 55-61 (Rus.).
113. Sonnabend, J. A., Martin, E. M., Mecs, E., and Fantes, L. H.: The effect of interferon on the synthesis and activity of an RNA polymerase isolated from chick cells infected with Semliki Forest virus, *J. Gen. Virol.*, 1:41-48, Jan. 1967.
114. Strander, H., and Cantell, K.: Production of interferon by human leukocytes *in vitro*, *Ann. Med. Exp. Fenn.*, 44:265-273, 1966.
115. Subrahmanyam, T. P., and Mims, C. A.: A study of the production source and action of interferon appearing in mice after the intravenous injection of influenza virus, *Brit. J. Exp. Path.*, 48:568-577, Oct. 1967.
116. Taylor, Joyce: Inhibition of interferon action by actinomycin, *Biochem. Biophys. Res. Comm.*, 14:447-451, 24 Jan. 1964.
117. Tilles, Jeremiah G.: Enhancement of interferon titers by poly-L-ornithine, *Proc. Soc. Exp. Biol. Med.*, 125:996-999, July 1967.
118. Todaro, G., and Green, H.: Simian virus 40 transformation and the period of cellular deoxyribonucleic acid synthesis, *J. Virol.*, 1:115-119, Feb. 1967.
119. Tokumaru, T.: The effect of trauma on production of Herpes interferon in guinea pigs, *Arch. fur die Gesamte Virusforsch.*, 21(1):61-70, July 1967.
120. Toy, S. T., and Gifford, G. E.: Loss of interferon activity from the medium of cell cultures producing interferon, *Nature*, 216(5110):82-83, 7 Oct. 1967.
121. Truden, J. L., Sigel, M. M., and Dietrich, L. S.: An interferon antagonist: its effect on interferon action in Mengo-infected Ehrlich ascites tumor cells, *Virology*, 33(1):95-103, Sep. 1967.
122. Tytell, A. A., Lampson, G. P., Field, A. K., and Hilleman, M. R.: Inducers of interferon and host resistance. III. Double-stranded RNA from reovirus type 3 virions (Reo. 3-RNA), *Proc. Nat. Acad. Sci.*, 58:1719-1722, Oct. 1967.

123. Vandeputte, M., DeLafonteyne, J., Billiau, A., and DeSomer, P.: Influence and production of interferon in Rauscher virus infected mice. *Arch. Ges. Virusforsch.*, 20:235-245, Mar 1967.
124. Vilcek, J., and Lowy, D. R.: Interaction of interferon with chick embryo cells, *Arch. Ges. Virusforsch.*, 21(2): 253-264, Sep. 1967.
125. Vilcek, J., and Ng, M. H.: Potentiation of the action of interferon by extracts of *Escherichia coli*, *Virology*, 31(3):552-555, Mar. 1967.
126. Waddell, D., Wilbur, J., and Merigan, T.: Interferon production in human mumps infections, *Proc. Exp. Biol. Med.*, 127:320-324, Jan. 1968.
127. Wagner, Robert: Interferon. A review and analysis of recent observations, *Amer. J. Med.*, 38:726-737, May 1965.
128. Wheelock, E. Frederick: Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin, *Science*, 149:310-311, 16 July 1965.
129. Wheelock, E. Frederick: Virus replication and high-titered interferon production in human leukocyte cultures inoculated with Newcastle Disease Virus, *J. Bact.*, 92(5):1415-1421, Nov. 1966.
130. Wheelock, E. Frederick: The effects of non-tumor viruses or virus-induced leukemia in mice: reciprocal interference between Sendai virus and Friend leukemia virus in DBA/2 mice, *Proc. Nat. Acad. Sci.*, 55:774-780, Apr. 1966.
131. Wheelock, E. Frederick: Effect of stralolon on Friend virus leukemia in mice, *Proc. Soc. Exp. Biol. Med.*, 124:855-858, Mar. 1967.
132. Wolstenholme, G. E., and O'Connor, M.: Interferon, Ciba Found. Symp., J. and A. Churchill, Ltd., London, 1968.
133. Wong, K., Baron, S., and Ward, T.: Rubella virus: role of interferon during infection of African green monkey kidney tissue cultures, *J. Immunol.*, 99:1140-1149, Dec. 1967.
134. Youngner, Jules S.: Interferon production in mice injected with viral and nonviral stimuli. *From Medical and Applied Virology*, edited by M. Sanders and E. Lannette, W. A. Green, Inc., St. Louis, Mo., 1968, pp. 210-222.
135. Youngner, J. S., Taube, S. E., and Stinebring, W. R.: Inhibition of viral replication by interferons with different molecular weights, *Proc. Soc. Exp. Biol. and Med.*, 123:795-797, Dec. 1966.

WHAT TO TELL THE PARENTS

What does one tell the parents of infants with intersex problems?

"I don't think anybody in the family should know. I don't tell the mother. I can imagine a situation arising where the daughter decides to run off with the chauffeur and the mother says, 'Well you can't; you're not even a girl,' in a family spat. In one or two cases where the patients have been told, there have been quite serious emotional problems. One of these girls was told, incidentally, and tried to commit suicide and another patient I know of did commit suicide. I think it is very important not to tell them."

—JOHN MCLEAN MORRIS, M.D., New Haven
Audio-Digest *Obstetrics and Gynecology*, Vol. 15, No. 3

MEDICAL STAFF CONFERENCE

Extrarenal Manifestations of Hypernephroma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. MAST*: This was the first University of California Medical Center admission of this 64-year-old Russian-born upholsterer. When admitted he had fever, anemia and congestive heart failure. One year before admission he was seen for an upper respiratory infection, and at that time no heart murmur was detected. Ten weeks before admission he noted easy fatigability and some dyspnea on exertion; and his wife noted that he was pale. Five weeks before admission he noted increased dyspnea on exertion, night sweats, and ankle edema. His private physician found his blood pressure to be 190/70 mm of mercury, and again no heart murmur was detected. Diuretics were prescribed and there was some subjective improvement. Two weeks before admission he again consulted his physician because of increasing edema, and dyspnea on exertion. Blood pressure at that time was reported at 160/70 mm. Hepatomegaly was noted. Following therapy with a digitalis preparation some improvement was noted. Shortly thereafter the patient was admitted to another hospital because of fever and anemia. When no cause for the fever was found he was transferred to the University of California San Francisco Medical Center.

The patient was pale, weak and anxious, with temperature of 37.4° C. The pulse was 88 beats

per minute, respirations 24 per minute and blood pressure 186/0 mm. There were no fundal hemorrhages. A 1.5 cm hard node was felt in the left supraclavicular area. The neck veins were engorged at 30° elevation. No cardiomegaly was detected although a grade IV/VI harsh systolic murmur was heard over the entire precordium, radiating into the neck. It was accompanied by a soft, grade II diastolic blowing murmur. The second sound over the aortic area was absent. Moist rales were heard over both lung bases. The liver was felt four fingerbreadths below the right costal margin. It was nonpulsatile and no rub was heard. The spleen was thought to be enlarged. Mild pretibial edema of the ankles was present. There were no splinter hemorrhages.

Laboratory data

Packed cell volume was 31 percent, leukocytes 18,600 per cu mm, sedimentation rate 60 mm per hour and the reticulocyte count was 0.8 percent. The urine was unremarkable and there were no significant abnormalities in the sediment. The alkaline phosphatase was 19 Shinowara-Jones-Reinhardt units, creatinine 1.6 mg per 100 ml, total protein 6.6 gm per 100 ml, prothrombin time 42 percent. An electrocardiogram showed digitalis effects only. The radiographic findings will be described by Dr. Preger.

*William Mast, M.D., Assistant Resident in Medicine.

On the day following admission, blood and bone marrow cultures were taken and because of the possibility of bacterial endocarditis, the patient was treated with large doses of intravenous penicillin and intramuscular streptomycin. Two days after admission a left supraclavicular node biopsy demonstrated probable metastatic renal cell carcinoma on frozen section. A radioactive liver scan performed on the same day showed a large defect in the right lobe of the liver (Figure 1) with multiple small defects throughout the liver. Despite therapy the patient remained febrile and quite ill. The circulation time was 16 seconds with a very poor end point. Intravenous pyelography showed a left renal mass. A femoral artery catheterization study revealed a cardiac output of 20 liters per minute. There was no evidence of aortic insufficiency or other aortic valvular involvement.

Three weeks after admission the patient became more obtunded, confused and lethargic. At that time serum calcium was found to be 13.2 mg and phosphorus 4.3 mg per 100 ml. He was treated with corticosteroids and hydration.

His course progressively deteriorated and he died one month after admission to hospital. Post-mortem examination demonstrated a large left hypernephroma which replaced most of the upper pole of the kidney. There were diffuse metastatic lesions in the liver and both pleural cavities but no evidence of cerebral or pulmonary metastasis. DR. PREGER*:¹ Intravenous pyelography (Figure

2) on the seventh hospital day showed a large mass in the upper two-thirds of the left kidney obliterating the calyces of the upper and mid-portion of the left kidney. A single distorted calyx and its infundibulum was seen at the lower pole. No calcification was present. The left adrenal gland was normal. The right kidney was depressed and rotated by enlargement of the liver.

The degree of calyceal visualization was less than usual due to a combination of raised serum creatinine (1.6 mg per 100 ml) and high output failure. An increased volume of contrast reagent (120 ml) was injected to compensate for this. A urogram indicated a renal cell carcinoma in the mid and upper portion of the left kidney. The enlarged liver was consistent with hepatic metastasis.

A chest radiograph on the 12th hospital day showed moderate generalized cardiomegaly, a left-sided pleural effusion and consolidation in the left lower lobe. A localized pleural density was present adjacent to the right seventh rib postero-laterally. This possibly represented metastatic spread, but no spread of lymphangitic type was present. On the day of death a chest radiograph taken with portable equipment showed bilateral pleural effusion and intra-alveolar fluid, either edema or blood, and a greater degree of cardiomegaly.

DR. SMITH*:² This patient represents an interesting and very important problem. I saw him early in his hospital course and concurred with the



Figure 1.—Liver scintophoto (right lateral view) demonstrating large defect in center of right lobe of liver.



Figure 2.—Intravenous pyelogram demonstrating enlargement of left kidney. The border of the left kidney is outlined by the dotted line.

*¹Leslie Preger, M.D., Assistant Professor of Radiology.

*²Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

clinical impression at that time, based on the heart murmur, weight loss, anemia and fever, that he probably had acute bacterial endocarditis. Dr. Richard Havel, who was the attending physician on the ward, may have concurred in this initial impression, but he insisted on early biopsy of the lymph node in the left side of the patient's neck. It was only after this biopsy that the true diagnosis became clear. There were still some unanswered questions pertaining to the clinical manifestations. Since the house staff did such an excellent job in elucidating this illness, we thought it most appropriate to call upon one of its members to lead the discussion. Dr. Edmund Lowrie, who is Senior Resident at the Moffitt Hospital, will review for us some of the manifestations in this case and comment more generally about some of the unusual manifestations of renal cell carcinoma.

Dr. Lowrie, among other problems, why was the cardiac output high?

DR. LOWRIE^{*3}: That is a very interesting question, Dr. Smith, and I hope that I can at least provide some theory to explain it. Creevy³ in reporting 92 cases of renal carcinoma from the University of Minnesota in 1935, wrote: "Malignant renal tumors should be classified with syphilis and tuberculosis as among the great mimics encountered in clinical medicine. By direct pressure, by necrosis or hemorrhage, by extension, by metastasis they can reproduce the clinical appearance of an amazing variety of disorders." We can now add to that list the production of several humoral syndromes.

I can think no better example of this could be put forth than the clinical problem encountered in the patient presented today. As Dr. Smith mentioned, a diagnosis of bacterial endocarditis was entirely reasonable as an initial impression. It was only the astute observation of supraclavicular lymphadenopathy and pursuit of this finding which produced a proper diagnosis.

Incidence and Pathological Findings

In 1958 the death rate from renal cell carcinoma was 2.91 per 100,000 population for Caucasians and 1.54 for Negroes. This neoplasm is usually encountered in persons over 40 years of age and, if Wilm's tumor is excluded, is twice as common in males as in females.¹ It accounts for about 75 to 85 percent of all renal cancers, the others being papillary carcinomas of the renal pelvis and meso-

thelial neoplasms. The right and left kidneys are involved about equally often. The upper and lower poles are each involved in 30 or 40 percent of cases, the mid-section in 20 or 30 percent.

Histologically these tumors are composed primarily of PAS-positive clear cells or PAS-negative granular cells, although both cell types are usually represented in any given tumor. In one recent series 63 percent were found to be of the clear cell variety, and 37 percent of the granular cell type. Hematuria was more frequent in association with granular cell carcinoma (65 percent against 46 percent), and with this type the prognosis is thought to be more serious. Systemic manifestations, on the other hand, were more common with clear cell carcinomas. Fever, for instance, was present in 30 percent. Erythrocyte sedimentation rate was also higher. Glycoproteins, haptoglobins and alpha 1 and 2 globulins have been noted to be elevated more often in clear cell carcinomas. Unless metastasis has occurred these factors have been noted to return toward normal with removal of the tumor.

Clinical Patterns of Presentation

Patients with renal cell carcinomas originally come to the physician for a variety of problems. Melicow and Uson in 1960⁸ reported a series of 577 patients and found that 32 percent had no urologic symptoms, or had atypical symptoms, when first seen. Sixty percent of these patients had never had hematuria. The classic triad of hematuria, flank pain, and flank mass is present in perhaps only 20 percent of all cases and two of these three manifestations are found in only 50 percent.

The presenting symptom complex falls into one or more of three broad categories: symptoms due to local complications, symptoms due to distant metastasis, or symptoms due to systemic manifestations. Locally the tumor may bleed or undergo infarction. Infarction may be manifest as pain, leukocytosis and fever. The renal vein is involved early, and this tumor may extend into it and into the vena cava as long, ropy cord. Varicocele has been noted in 3 percent of left renal carcinomas because of drainage of the left spermatic vein into the left renal vein. Pampiniform plexus thrombophlebitis has been a presenting problem. So has vena caval thrombosis, with pulmonary embolism occurring as a complication. Ureteral colic has been reported as a presenting complaint, due to the passage of clot or tissue. Following an infarc-

^{*3}Edmund Lowrie, M.D., Senior Resident in Medicine.

tion, the tumor may become the site of a perinephric or renal abscess.

The incidence of distant metastasis at the time of initial diagnosis is difficult to determine. Approximately 40 percent is a reasonable figure. In one series in which 273 patients presented primarily with non-urolological symptoms, 10 percent sought the aid of a physician because of symptoms arising from metastasis.² Bone is considered to be the most common site for symptomatic metastasis, but in pathologic series the lung is the most common site of involvement. About 50 to 60 percent of patients have metastatic lesions of the lung at autopsy. Next most frequent sites of metastatic spread are liver, bone, regional nodes and brain, with an incidence of approximately 30 percent each. The reason for this disparity is probably related to the incidence of bone pain and fracture. In one series, 17 percent of the patients who presented with non-renal symptoms complained of pain other than flank pain.⁸ In the same series 7 percent presented with symptoms primarily referable to lung metastasis—namely, cough, dyspnea, hemoptysis or the expectoration of tissue. In at least one case this tissue was found to be morphologically compatible with renal adenocarcinoma. Nodules may be noted in an x-ray film of the chest taken during a routine physical examination. The tumor may also present as a metastatic nodule in a variety of other tissues including supraclavicular lymph nodes, the recto-vaginal septum, the retro-orbital tissue, the tongue, the mouth, skin and the phallus. It is also of interest that metastasis from these tumors to the bladder and ureter sometimes occurs. An intrascrotal mass may not be a testicular carcinoma, but a metastatic renal carcinoma. Incidentally, this is the commonest neoplasm metastatic to the thyroid gland.

Systemic Manifestations

The third method of presentation is that of systemic manifestations. In the patients studied by Melicow and Uson⁸ 50 percent presented with symptoms that may be described as those of general ill health—weakness, anorexia, weight loss, anemia and general disability. Fever can be a perplexing problem. The association of fever and renal carcinoma was first described in 1887, and the incidence varies greatly with the series. In a report from the Mayo Clinic in which some 1,200 cases were reviewed, fever was present in 11 percent and was the sole presenting symptom in 2

percent.¹¹ If one averages the nine series which comment on fever, the incidence is about 17 percent. The basic pattern is thought to be a low grade fever, but it may be quite high and spiking in character, suggesting Hodgkin's disease or sepsis. Fever was once thought to be due to necrosis of the tumor. There are many cases on record, however, in which the tumor was small and non-metastatic, and at operation no necrosis was found. In the patient presented today, fever and leukocytosis may well have been due to necrosis, as there was ample necrosis present on pathological sections of the tumor.

Polycythemia has been noted by Damon to be present in about 2.5 percent of patients with renal cell carcinoma.⁴ Of 205 patients with polycythemia, he found 4 percent with cancer of the kidney. This is usually erythrocythemia rather than true polycythemia. The coincidence of leukocytosis, thrombocytosis, erythrocytosis and splenomegaly has been recorded in several cases. In the absence of metastasis, erythrocythemia frequently disappears when the tumor is removed. It may return with the appearance of metastasis, and furthermore is known to have antedated the diagnosis of the tumor by as long as three years. Erythrocythemia probably results from excessive production and secretion of erythropoietin. This is not surprising, for the kidney has been demonstrated to be the major source of this hormone. Erythropoietin-like substances have been isolated from renal cell carcinomas. A similar substance has been found in cerebellar hemangioblastomas, another tumor associated with erythrocythemia. There are at least 20 cases in which the coincidence of cerebellar hemangioblastoma or Von Hippel-Lindau's disease and renal cell carcinoma was noted.

Hypercalcemia has been estimated to be present in 10 percent of patients with clear cell tumors. Bone metastasis is frequent and may explain some hypercalcemic complications. In many instances serum chemical features resemble those of hyperparathyroidism, with increased serum calcium, decreased serum phosphorus, decreased tubular reabsorption of phosphorus and increased alkaline phosphatase. In the cases reviewed by Pinals and Krane, serum calcium returned to normal in eight or nine patients following surgical removal of the tumor.¹⁰ Since that time more cases have been described. Recently an immuno-reactive parathyroid peptide was demonstrated in such tumors as the probable cause of reversible hypercalcemia.⁹ These patients therefore have hyperparathyroid-

ism, but with the excessive hormone deriving from the tumor rather than from the parathyroid glands.

The association of amyloidosis with kidney tumor was well reviewed as early as 1946.⁵ This is usually of the secondary or perireticulin type. While the depositions are usually discovered at postmortem examination, a distinctive clinical syndrome has been described consisting of unilateral renal mass and rapid downhill course from uremia, especially with heavy proteinuria. Hepatosplenomegaly may be present, but this is not invariably so.

In large series of patients with renal carcinoma, elevated alkaline phosphatase levels are sporadically mentioned, but no true incidence can be discovered. Possible reason for such an elevation are bone or hepatic metastasis, of course, and in the patient presented today hepatic metastasis was noted. In 1961, Stauffer reported in abstract five patients without metastasis but with increased alkaline phosphatase, abnormal bromsulphalein retention, decreased albumin and abnormal prothrombin time determinations. Since that time at least three more such cases have been recorded. In at least three of this total of eight patients, the abnormality in liver function tests remitted when the tumor was removed. Liver biopsy frequently is normal but may show a mild lymphocytic infiltration. The cause of this reversible hepatic dysfunction remains unexplained.

Electrophoresis of serum alkaline phosphatase has demonstrated increased fractions in the beta-1 and beta lipoprotein regions at the origin. This pattern was interpreted by Taswell to be consistent with liver parenchymal disease. Dr. Paul Holland, currently with our program, has suggested that the non-metastatic hepatopathy of renal carcinoma has been overlooked for many years and that a more diligent search is in order.⁶

High Output State

A hypernephroma is usually a very vascular tumor, and arteriovenous shunts with high cardiac output have been reported.⁷ Indeed a pulsating tumor mass in an adult patient should suggest the possibility of metastatic renal cell carcinoma or carcinoma of the thyroid. Shunts with high output have also been noted with bony and visceral metastasis. Removal or irradiation of the tumor may reverse the high cardiac output. In the patient presented today a tumor arterio-venous shunt may have accounted in part for the pronounced high

output state. A suggestion of hepatic hemangiomas on preliminary pathological sections was noted and aneurysmal dilatation of sinusoids was present. Other possible causes in this patient include fever and anemia. At the time of the cardiac output measurement, however, his temperature was normal. There is one other fascinating aspect, and that concerns hypermetabolism. Our patient was found to have an oxygen uptake of about 350 cc per minute. This corresponds to a metabolic rate in a man of his size and age of plus 58 percent. We cannot pretend that our patient was in a basal state at the time of this determination, although he was at rest. The peripheral vascular resistance in this patient was low with increased flows, and the systemic arterio-venous oxygen difference was reduced approximately 17 ml per liter. The arterio-venous oxygen difference across the splanchnic bed was normal, however. Therefore he had a normal arteriovenous oxygen difference with increased blood flow across a bed which contained a great deal of tumor. The massively cancerous liver may have been the source of a pronounced increase in the metabolic demands of this patient and may have contributed to the high cardiac output.

Other Clinical Manifestations

The association of Cushing's syndrome with renal carcinoma has been recorded in three patients. One of these patients had an adrenal adenoma. The other two had adrenal hyperplasia, but in one of these Cushing's syndrome was diagnosed 21 years before the diagnosis of the renal tumor. Therefore the association of renal cancer with ACTH production remains highly speculative.

A salt-losing syndrome was described in one patient. This patient presented with profound hyponatremia and hypovolemia. As much as eight liters of fluid and 1,100 mEq of sodium per day could not keep pace with his losses. A renal mass was noted, and split renal function studies revealed one normal kidney. The other had a creatinine clearance of 8 ml per minute and excreted about 6 to 8 liters of fluid per day with a composition similar to plasma. After nephrectomy the salt-losing syndrome abated.

In addition to neurologic manifestations from metastasis, one case of peripheral neuropathy and one of myopathy have been recorded. In one interesting case the patient had primary pulmonary hypoventilation marked by normal breathing mechanics and carbon dioxide unresponsiveness

TABLE 1.—*Complications of Hypernephroma*

Local complications:
Hemorrhage and infarction
Venous thrombosis
Hydronephrosis and ureteral colic
Infection
Complications caused by metastases in:
Lung
Bone
Liver
Lymph nodes
Brain
Systemic complications:
Fever
Erythrocythemia
Hypercalcemia
Amyloidosis
Hepatomegaly
Cushing's Syndrome
Osteoarthropathy
Neurologic complications

of the respiratory center. Nephrectomy produced definite remission.

There is at least one case on record of clubbing of the fingers coincident with renal tumor, and removal of the tumor produced regression of this

deformity. As far as I am aware, hypoglycemia and inappropriate secretion of antidiuretic hormone, gonadotropins or thyrotrophin have not been described with this disease.

We might return then to Creevy's original notion of some 32 years ago and say that renal cell carcinomas, indeed, may well represent one of clinical medicine's great mimics.

REFERENCES

1. Arner, O., Blanck, C., and Schreeb, T.: Renal adenocarcinoma; morphology—grading of malignancy—prognosis. A study of 197 cases, *Acta Chir. Scand. Suppl.*, 346:1-51, 1965.
2. Berger, L., and Sinkoff, M. W.: Systemic manifestations of hypernephroma: A review of 273 cases, *Amer. J. Med.*, 22:791-796, 1957.
3. Creevy, C. D.: Confusing clinical manifestations of malignant renal neoplasms, *Arch. Int. Med.*, 55:895-916, 1935.
4. Damon, A., Holub, D. A., Melicow, M. M., and Uson, A. C.: Polycythemia and renal carcinoma. Report of 10 cases, two with long hematologic remission following nephrectomy, *Amer. J. Med.*, 25:182-197, 1958.
5. Hyman, A., and Leiter, L. E.: Association of hypernephroma with amyloidosis of the kidney, *J. Urol.*, 56:303-309, 1946.
6. Lemmon, W. T., Holland, P. V., and Holland, J. M.: The hepatopathy of hypernephroma, *Amer. J. Surg.*, 110:487-91, 1965.
7. Maldonado, J. E., Sheps, S. G., Bernatz, P. E., Deweerd, J. H., and Harrison, E. G. Jr.: Renal arteriovenous fistula. A reversible cause of hypertension and heart failure, *Amer. J. Med.*, 37:499-513, 1964.
8. Melicow, M. D., and Uson, A. C.: Nonurologic symptoms in patients with renal cancer, *JAMA*, 172:146-51, 1960.
9. O'Grady, A. S., Morse, L. J., and Lee, J. B.: Parathyroid hormone-secreting renal carcinoma associated with hypercalcemia and metabolic alkalosis, *Ann. Intern. Med.*, 63:858-68, 1965.
10. Pinals, K. S., and Krane, S. M.: Medical aspects of renal carcinoma, *Postgrad. Med. J.*, 38:507-19, 1962.
11. Weinstein, E. C., Geraci, J. E., and Greene, L. F.: Hypernephroma presenting as fever of obscure origin, *Proc. Mayo Clin.*, 36:12-19, 1961.



CASE REPORTS

Pulmonary Coccidioidomycosis

The Wide Spectrum of Roentgenographic Manifestations

RONALD A. CASTELLINO, M.D., AND
NORMAN BLANK, M.D., *Palo Alto*

COCCIDIOIDOMYCOSIS IS PRIMARILY a self-limited pulmonary disease caused by the fungus *C. immitis*. It uncommonly progresses to the potentially fatal disseminated form. The fungus exists in sharply demarcated areas, mainly the southwestern United States, northern Mexico, and the Gran Chaco region in South America, where the disease is endemic. Rare documented cases due to fomite transmission¹ have been reported. Because rapid modern travel permits a person to first manifest coccidioid illness in non-endemic areas, clinicians and radiologists everywhere are potentially confronted with diagnosis of this disease. Epidemiology, clinical manifestations, skin and serological testing, pathology and treatment have been dealt with in the literature.*

There is, however, a paucity of information in the literature documenting the conversion of the x-ray film of the chest, during clinical coccidioid disease, from normal to abnormal. Most reports concern ill patients in whom initial x-ray films demonstrated abnormal findings due to coccidioidomycosis. A recent case, in which the transition from a normal x-ray film to one showing gross dis-

ease occurred rapidly during symptomatic illness, seemed of sufficient interest to warrant a detailed report, since no other documented case has previously been reported and illustrated. This case stimulated us to review all cases of pulmonary coccidioidomycosis at the Palo Alto-Stanford Hospital and the Palo Alto Veterans Administration Hospital within the past six years, with a view to defining and describing the various manifestations.

Report of a Case

A 44-year-old man of Indian and Spanish descent had sudden onset of right pleuritic pain in the chest on 19 September 1966. He was admitted to hospital and a chest film made at that time (Figure 1A) was normal. Several days previously he had had a bout of malaise and night sweats. Eight days previously he had spent the weekend in the San Joaquin Valley.

Three days after admission, on 22 September, productive cough, malaise and fever developed. A chest film (Figure 1B) showed the rapid appearance of multiple bilateral subsegmental infiltrates as well as superior mediastinal widening indicating adenopathy. A coccidioidin skin test was positive at 1:100 as was intermediate purified protein derivative (PPD). Because of the appearance of icterus and biochemical evidence of liver impairment, liver biopsy was performed. It revealed several granulomas with many eosinophils and was interpreted as non-specific. No culture was obtained. Subsequent complement fixation for coccidioidomycosis was positive at 1:32 dilution, and precipitins were positive at 1:10. The combination of the elevated serological titres, in conjunction with the liver granulomas, established the diagnosis of acute disseminated coccidioidomycosis. The only pertinent physical findings were occasional rales at the right base.

Treatment with amphotericin B was begun 18 October and within two weeks the fever and symptoms had resolved. The patient then remained

*Reference Nos. 3,7-11,18,19,21,22,24,25,27,28.

From the Department of Radiology, Stanford University School of Medicine, Palo Alto.

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Reprint requests to: Department of Radiology, Stanford Medical Center, 300 Pasteur Drive, Palo Alto 94304 (Dr. Castellino).

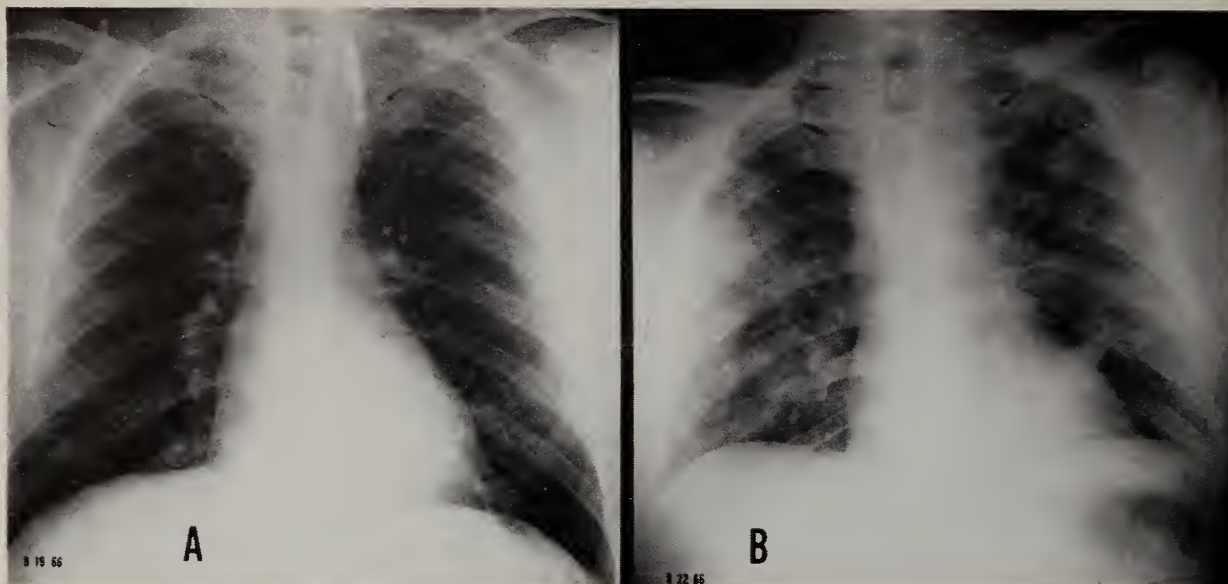


Figure 1.—A. During clinical illness (previous malaise and night sweats, current chest pain) the chest film is normal. Streak paralleling medial end of left clavicle is an artifact. B. Three days later, bilateral ill-defined patchy infiltrates corresponding with the clinical appearance of productive cough, malaise and fever. There is also widening of the superior mediastinum secondary to adenopathy.

asymptomatic. Follow-up chest films were obtained. On 24 October (Figure 2C) there was persistent mediastinal adenopathy and the parenchymal nodular components had become more discrete and better defined. On 19 December (Figure 2D) there was apparent resolution of the mediastinal adenopathy. The parenchymal nodules had decreased in size and number. Complement fixation titres were 1:64 in October 1966, 1:256 in November 1966, and 1:32 in January 1967.

Analysis of Case Studies

Forty proven cases of coccidioidomycosis at the Palo Alto-Stanford Hospital and the Palo Alto Veterans Administration Hospital were reviewed. These cases clearly demonstrated the wide radiologic spectrum of pulmonary involvement, and particularly the degree to which this disease can mimic other lesions such as carcinoma of the lung. In addition, the literature was reviewed with re-

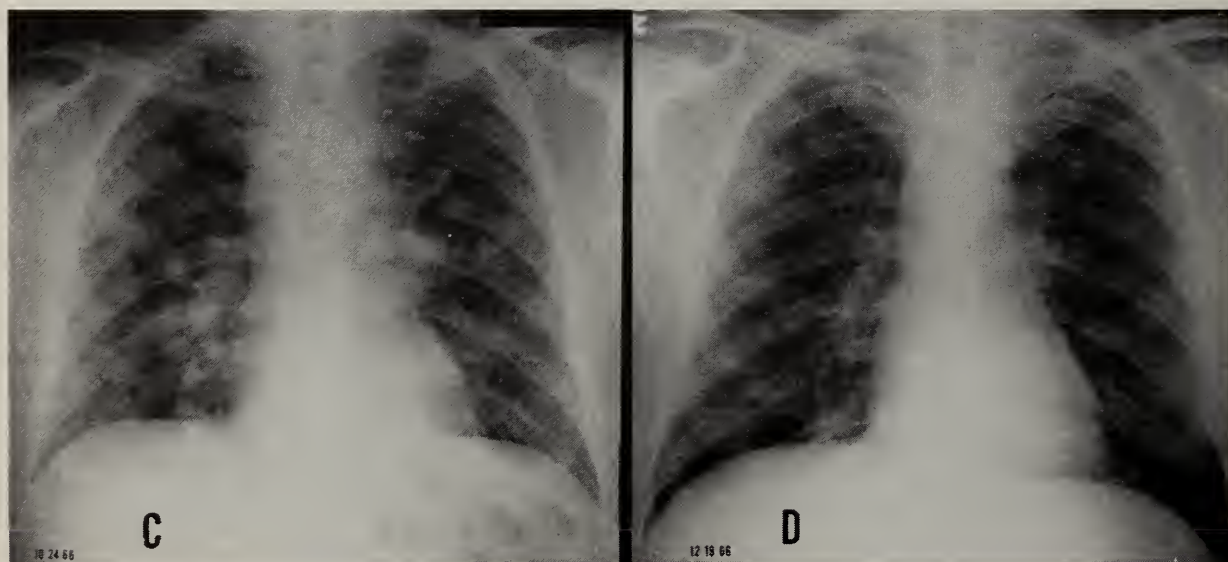


Figure 2 (same case as Figure 1).—C. Approximately one month later there is no change in the superior mediastinal adenopathy. The nodular infiltrates, however, have become better defined and are more discrete. D. Two months later there is resolution of the mediastinal adenopathy. The parenchymal nodules persist, although they have become less numerous and smaller.

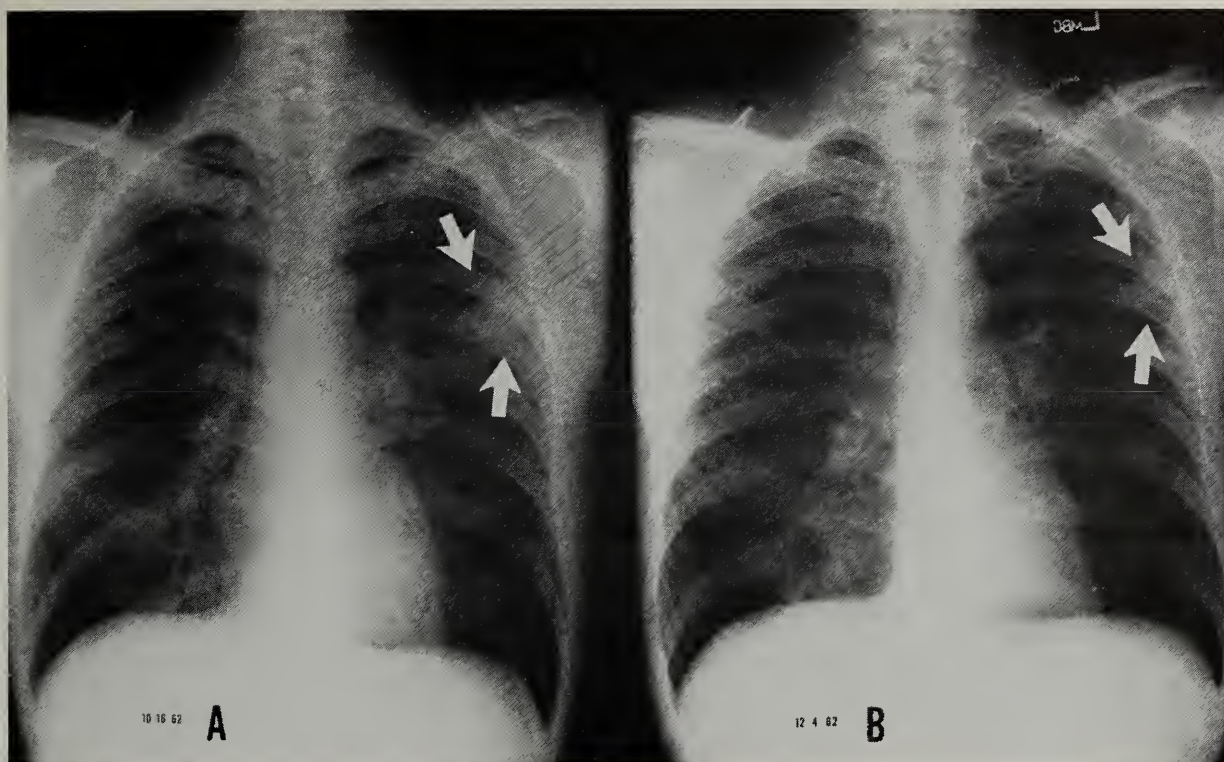


Figure 3.—The patient is a 31-year-old white man from San Joaquin Valley with multiple previous episodes of “pneumonia,” hemoptysis and chest pain. Previous chest x-ray films and bronchograms, most recently of August 1962, were negative. Chest x-ray film (A) in October 1962 showed appearance of left hilar adenopathy and a peripheral infiltrate in the left upper lobe. PPD and coccidioidin skin tests were positive. Complement fixation for coccidioidomycosis was positive at 1:2 dilutions. Follow-up x-ray film (B) almost two months later shows interval minimal decrease in the left hilar adenopathy and pronounced decrease in the left upper lobe infiltrate. (Note: Infiltrate at right base 12/4/62 was due to transient aspiration pneumonia following scalene node biopsy.) On 12/20/62, thoracotomy confirmed active coccidioidomycosis in the left upper lobe with subsequent positive cultures.

spect to the radiographic findings, and the following impressions were obtained.

Acute Radiographic Manifestations^{4,6,10,15,20}

“Pneumonic” infiltrate and consolidation. This is by far the most common type of involvement and is present in the acute stage in over one-half of cases. Since the initial pathologic process is bronchitic, a peribronchial infiltrate imparting a fuzzy and thickened appearance to the hilar pulmonary markings may be seen. Fan-shaped infiltrates radiating from the hila to the periphery are also apparent as are patches of relatively well circumscribed parenchymal infiltrates (Figures 3 and 5). Areas of consolidation, usually segmental or subsegmental, commonly develop. There may be single or multiple areas of parenchymal involvement, and they can be located anywhere in the lung. During this acute phase, the parenchymal densities at times demonstrate transient cavitation,¹⁶ particularly when tomography is used. These “phantom cavities” probably represent areas of over-inflated lung due to check valve mechanisms⁸ and are not

synonymous with the chronic residual cavity. The parenchymal densities can resolve within days to several weeks, but often the clearing occurs over months.

Adenopathy. Hilar and mediastinal adenopathy is commonly seen. It is usually associated with parenchymal changes and severe clinical disease. At times, however, the adenopathy may be the only radiographic manifestation (Figure 4). In such circumstances “pneumonic” changes may have been present and cleared by the time of the first x-ray film. The hilar nodes are more commonly involved than the mediastinal nodes and usually return to normal sooner. Mediastinal adenopathy appears to accompany more severe infections and is probably associated with a greater risk of dissemination. Adenopathy, particularly mediastinal, may persist for a month to years.

The combination of parenchymal disease and adenopathy, especially when unilateral, is indistinguishable radiographically from bronchogenic carcinoma (Figures 3, 5, and 10). In addition, coccidioidal adenopathy can cause bronchostenosis

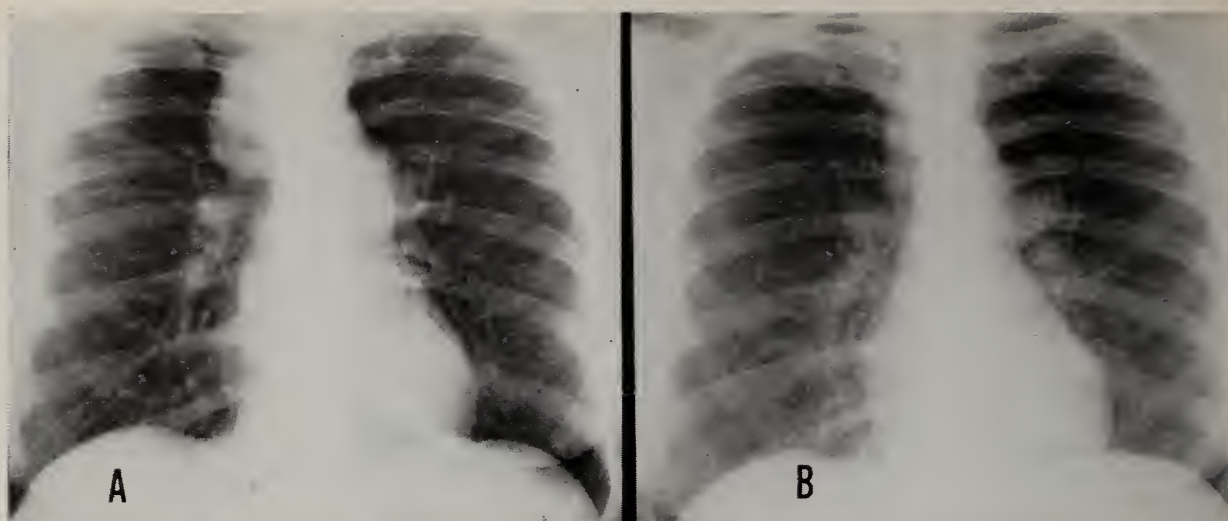


Figure 4.—Patient is a 33-year-old white woman who went rock hunting near Coalinga, California, in October 1963. Shortly thereafter dry-to-productive cough developed and lasted until January 1964. Early in January 1964, patient noted an enlarged left axillary node which progressively increased in size. In March 1964 biopsy of the node was carried out and *C. immitis* was recovered. Coccidioidin skin test was positive, complement fixation was positive at 1:64 and precipitins were negative. Chest x-ray film (A) showed massive mediastinal adenopathy with no parenchymal abnormalities. A total of 4.9 grams of amphotericin B was given. Serial chest x-ray films and complement fixation determinations showed progressive regression. The most recent film (B) taken in October 1966, shows decidedly decreased but persistent adenopathy after two and a half years. Complement fixation at this time was 1:2.

(Figure 9) mimicking the bronchial lesion of carcinoma. The regression of adenopathy favors coccidioidal disease although rarely this may also occur as inflammatory adenopathy subsides during treatment of peripheral pneumonia in cases of obstructing bronchogenic carcinoma.

Miliary and nodular parenchymal involvement.

True miliary involvement is due to hematogenous dissemination and the prognosis is poor if untreated. The miliary pattern can present initially in the course of the disease or at any subsequent period (Figure 6). The x-ray appearance is indis-

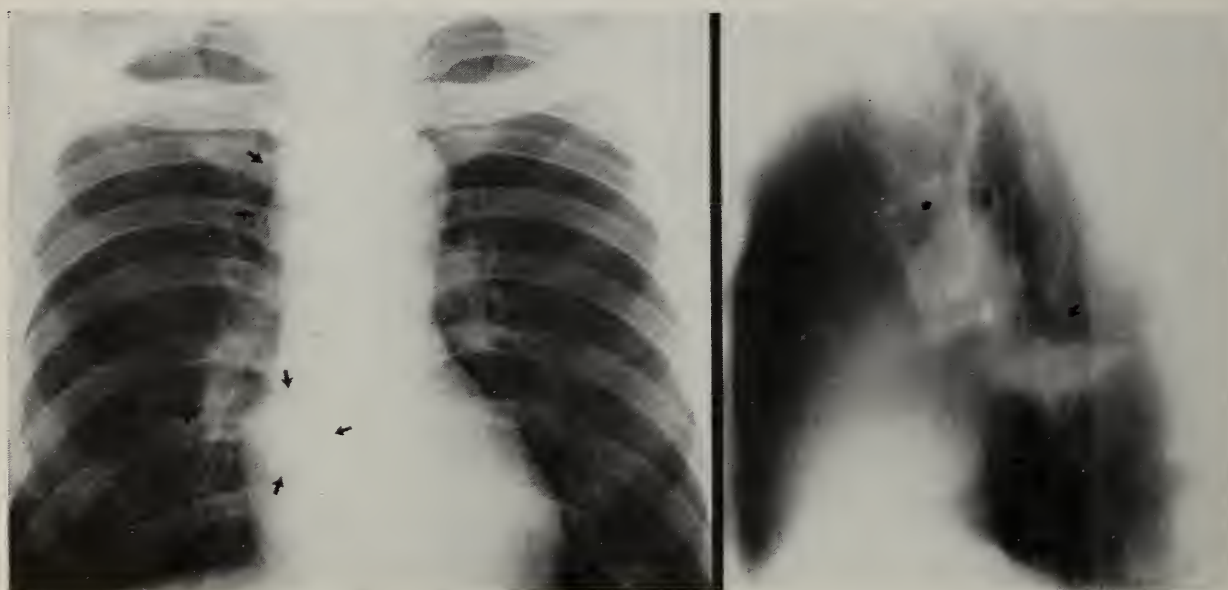


Figure 5.—The patient is a 47-year-old Negro man who had right coronary endarterectomy in April 1962. Reevaluation in December 1962 revealed malaise, dry cough, chest discomfort and weight loss over several weeks. Chest x-ray studies showed presence of right paratracheal adenopathy (upper arrows), right hilar adenopathy (middle arrows), and a dense infiltrate in the subsegment of the RLL (lower arrows), which had not been present previously. Lateral tomogram demonstrates the infiltrate in the right lower lobe more clearly. Sputum cultures and bronchoscopy were negative. Coccidioidin skin test was strongly positive (5 cm induration), as was tuberculin skin test. Coccidioidal complement fixation was positive at 1:8 dilution, precipitins at 1:10. The patient had lived in the San Joaquin Valley for three months before admission. Supportive therapy was given.

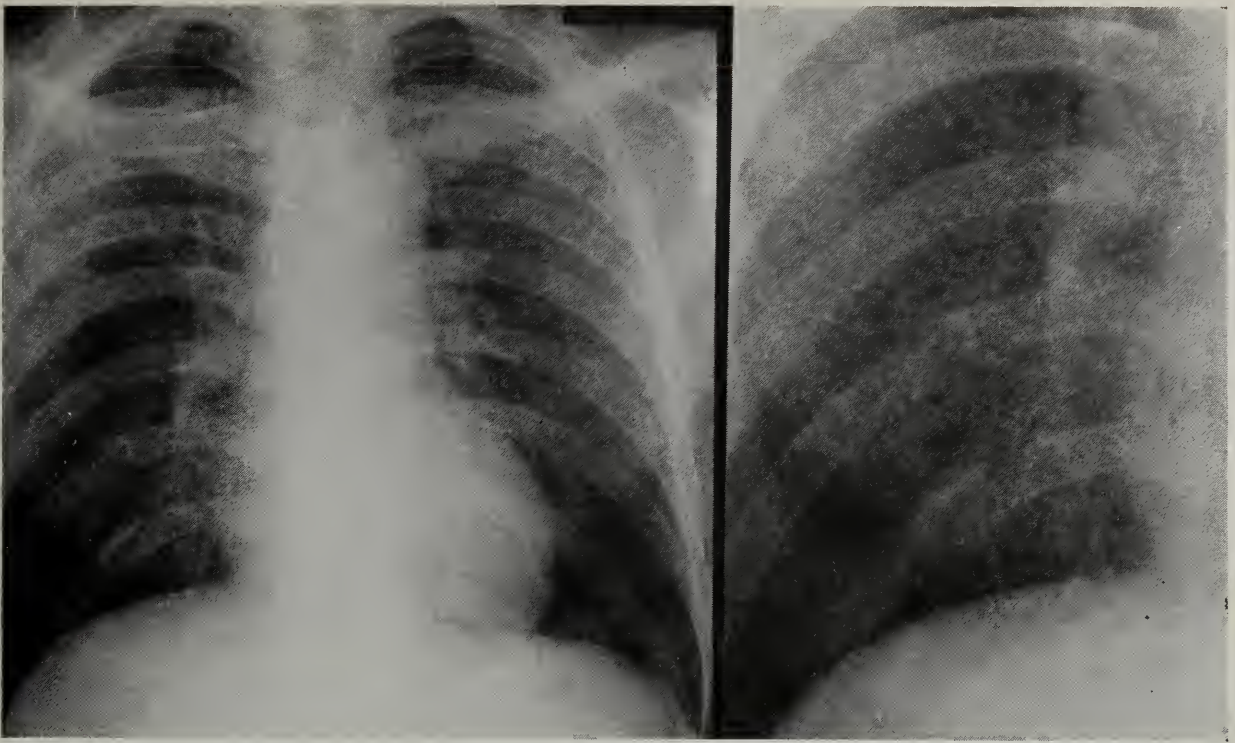


Figure 6 (same case as Figure 5).—Readmitted 28 December 1964, with fever, night sweats, 40 pound weight loss and right hip pain. X-ray film of chest showed a diffuse miliary pattern involving both lung fields. A magnified detailed view of the right lower lung is included. The coccidioidin skin test was now negative at 1:100 and 1:10 dilutions, indicating anergy. The complement fixation was 1:256 initially, and rose to 1:1024 in two months. Amphotericin B was begun on 5 January 1965. Culture of aspirate from right hip produced *C. immitis*. Follow-up chest films showed gradual resolution and almost two years later was essentially normal. Complement fixation 1:256 at two years.

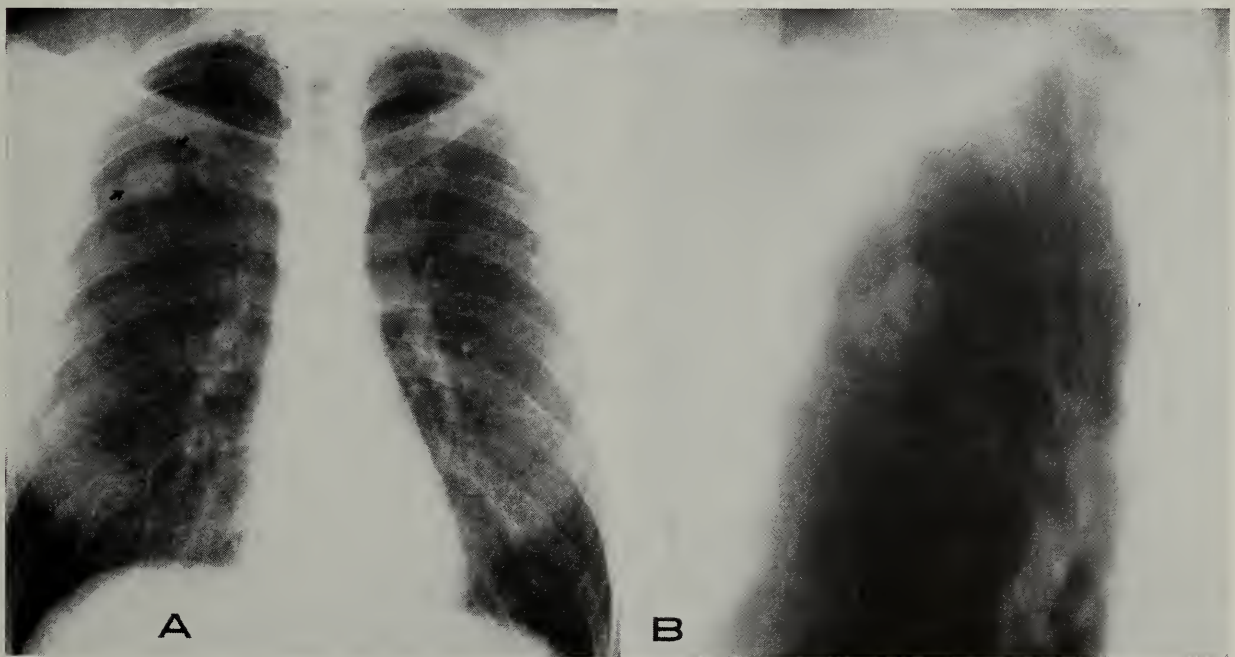


Figure 7.—The patient, a 30-year-old white man had a chest roentgenograph because of a minor injury to the right shoulder. It showed (A) a "coin lesion" in the right upper lobe, with no other abnormalities. Figure B is a frontal tomogram of the lesion. Except for minor pain due to the trauma, the patient was asymptomatic. He had lived in the San Joaquin Valley two and a half years earlier. Complete work-up, including bronchoscopy, sputa for fungi, and coccidioidin skin tests were all negative. Thoracotomy revealed a nodule in the right upper lobe which contained spherules with endospores and septate hyphae which on culture yielded *C. immitis*.

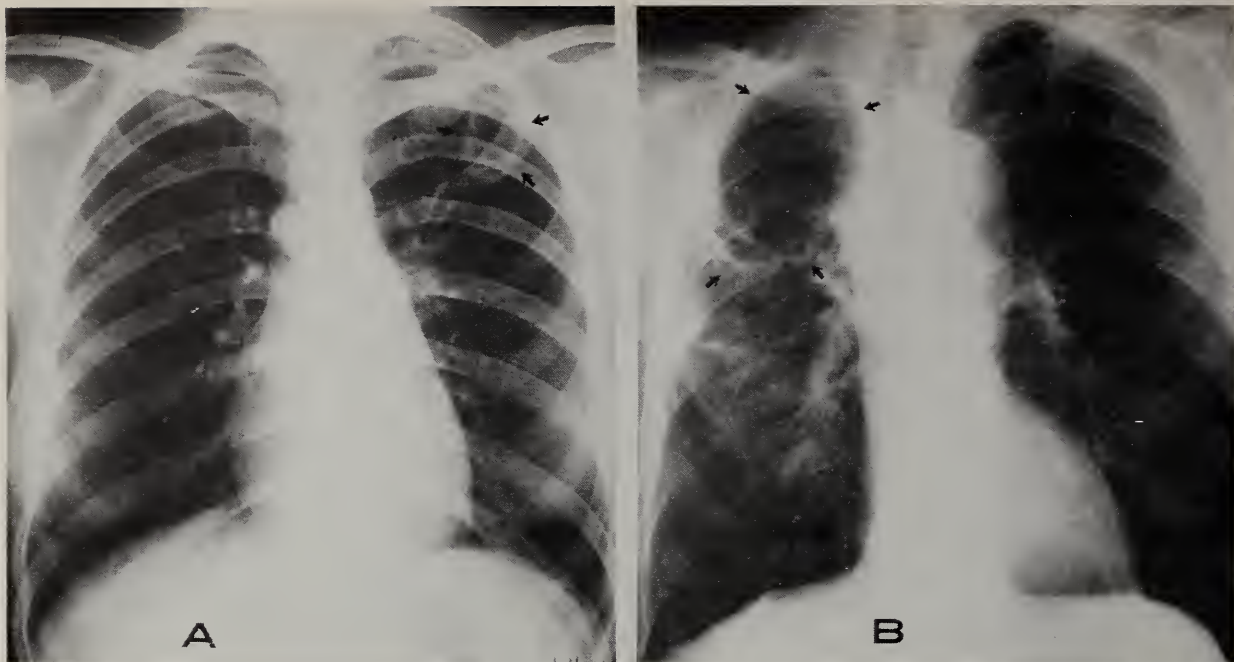


Figure 8.—X-ray film (A) of chest of 21-year-old woman, taken because of a heart murmur noted during a routine physical examination, showed a well-defined cavity in the left upper lobe (arrows) with no apparent surrounding parenchymal changes. Also noted is a calcified primary complex on the right. Skin test and sputum cultures for coccidiomycosis were positive. Thoracotomy revealed a thin-walled, 1.5 cm diameter cavity which, at microscopy, showed granulomas containing *C. immitis*. (B) X-ray film of chest of 69-year-old white man admitted with "arthritis" in November 1960, shows a massive right upper lobe cavity which was not present on previous films. In addition, the film shows areas of parenchymal infiltrate and obstructive airway disease. Over the preceding four to five months he had had a 33 pound weight loss, increasing dyspnea, and productive cough. He had lived in the Fresno Valley for 15 years but denied previous "valley fever." Coccidioidin skin test was positive (18 mm) as was PPD (15 mm). Numerous smears and cultures were negative for tubercle bacillus. *C. immitis* was recovered from sputa and bronchial washing. Bronchoscopy showed chronic endobronchitis. Complement fixation was positive at 1:4 and precipitins were negative. Patient died in August 1961 from unrelated causes. Autopsy revealed a large right upper lobe cavity traversed by fibrosed trabeculae with *C. immitis* spherules. There was no evidence of dissemination.

tinguishable from that of miliary tuberculosis.

A different radiographic appearance is that of diffusely scattered nodular densities similar to those seen in metastatic carcinoma to the lungs. Whether this represents true dissemination is debatable; some investigators²⁰ feel that this appearance may be related to aspiration of infected sputum from an initial infection to other parts of the lung. If a recent "normal" chest x-ray is available for comparison (Figures 1 and 2), the rapid appearance of this parenchymal involvement favors a non-neoplastic etiology.

Pleural involvement. Pleural changes are less common and are seen in from 2.7 to 5 percent of cases. One observer¹⁷ said that there is pleural effusion, usually only minimal blunting of a gutter, in 20 percent of acute cases. In some 2 percent, however, there is moderate to massive effusion with or without associated parenchymal involvement. These large effusions can clear in several weeks or persist for over a year.

Radiographic Manifestations of Chronic Disease^{2,4,10,13,14,19,23}

In about 5 percent of cases with positive chest films residual changes will develop. The most common of these are cavities and solid nodular foci. A chronic benign residual change has been defined¹³ as any pulmonary lesion persisting for three or more months after acute pulmonary coccidioidomycosis without evidence of dissemination. A certain proportion of these cases will show slow resolution over a more prolonged period. Once again, there is no pathognomonic or characteristic x-ray appearance.

Nodular parenchymal foci (coccidioidoma). These account for more than one-third of all chronic residual changes and develop in areas of previous infiltrate or consolidation. They may also result from "filling-in" of a cavity. They are usually discrete, round, average 2 cm in diameter, and commonly are located subpleurally and in the upper lung fields (Figure 7). Over 90 percent are located more than 5 cm from the hilar area. They

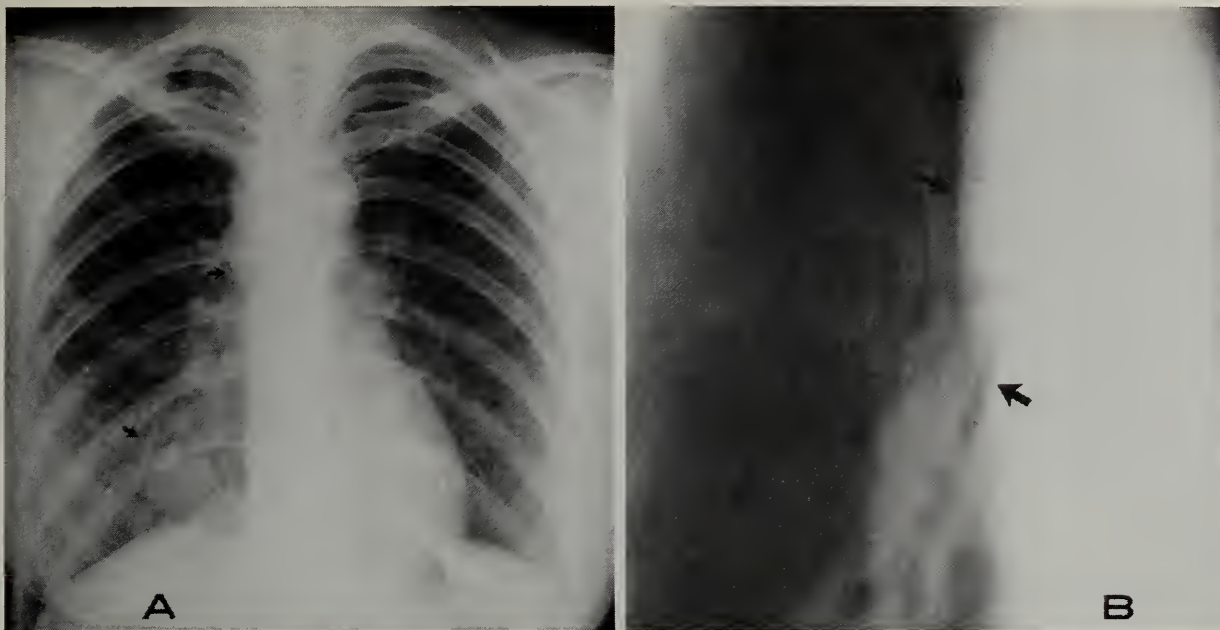


Figure 9.—The patient is a 27-year-old woman with cough, chest pain and intermittent fever for one year. Chest x-ray showed right paratracheal adenopathy (upper arrows), fullness of the right hilum, and infiltrate at the right base. A frontal tomogram demonstrates narrowing of the bronchus intermedius (lower arrow). Upper arrows outline paratracheal adenopathy. Bronchoscopy revealed occlusion of the right middle lobe orifice by biopsy-proven granulation tissue. Tissue cultures yielded *C. immitis*. Complement fixation was positive at 1:32, as was the precipitins at 1:10.

develop in an average of five to six weeks, can contain calcification and are almost always single. The differential diagnosis is that of the "coin lesion." Bronchogenic carcinoma may be simulated, especially when the coccidioidoma is associated with residual coccidioid adenopathy. Whereas in non-endemic areas some 30 to 50 percent of all "coin lesions" proved to be malignant, if a patient with a "coin lesion" gives a history of having lived in an endemic area and if, in addition, the coccidioidin skin test is positive, the likelihood of malignant disease is reportedly less than 2 percent.⁸

Cavitation. A cavity is a commoner form of chronic residual change than is coccidioidoma. The typical "thinned-walled" cavity with little or no surrounding reaction usually develops from areas of previous parenchymal infiltrate. The "thick-walled" cavity is more often the result of excavation of solid nodular foci. These cavities average 2 to 3 cm in diameter (Figure 8A) and are usually discrete and round. Sometimes, however, the residual cavity may attain great size (Figure 8B). The usual location is in the upper lung field in a subpleural position and at some time they may contain fluid. Winn's²⁶ outstanding ten-year study of 92 patients with cavities, half of them observed longer than five years, showed that 25 percent resolved spontaneously, 6 percent

filled in to form solid foci, 10 percent persisted without harm to the patient, and 2 percent ruptured with ensuing pneumothorax with and without empyema. Fourteen patients had resection and one-third had collapse therapy for symptoms of frequent hemoptysis or increasing cavity size. Forsee¹² resected 30 cavities and found mycelia in 15 and spherules on tissue section in 26.

Persistent coccidioid pneumonia and/or adenopathy (Figures 9 and 10). In Jamison's¹⁴ series of 96 chronic cases, 21 patients had persistent infiltrates and in six cases these lesions were associated with pronounced hilar and/or mediastinal adenopathy. In two other cases only adenopathy was demonstrated. In another series,¹⁹ of 100 cases, there were eight with predominately residual pneumonia and seven of predominately residual adenopathy. Resolution is slow and gradual (Figure 4); the adenopathy often outlasts the infiltrate.

Other residual lesions. Significant residual pleural effusions were seen in about 2 percent of chronic cases; in two of three reported cases¹⁴ they required over a year to resolve. Chronic coccidioid empyema may follow a pleural effusion or may result from rupture of a peripherally located cavity. Cavity rupture can also cause pneumothorax, hydropneumothorax and broncho-pleural fistula. Residual pulmonary fibrosis in an area of previous

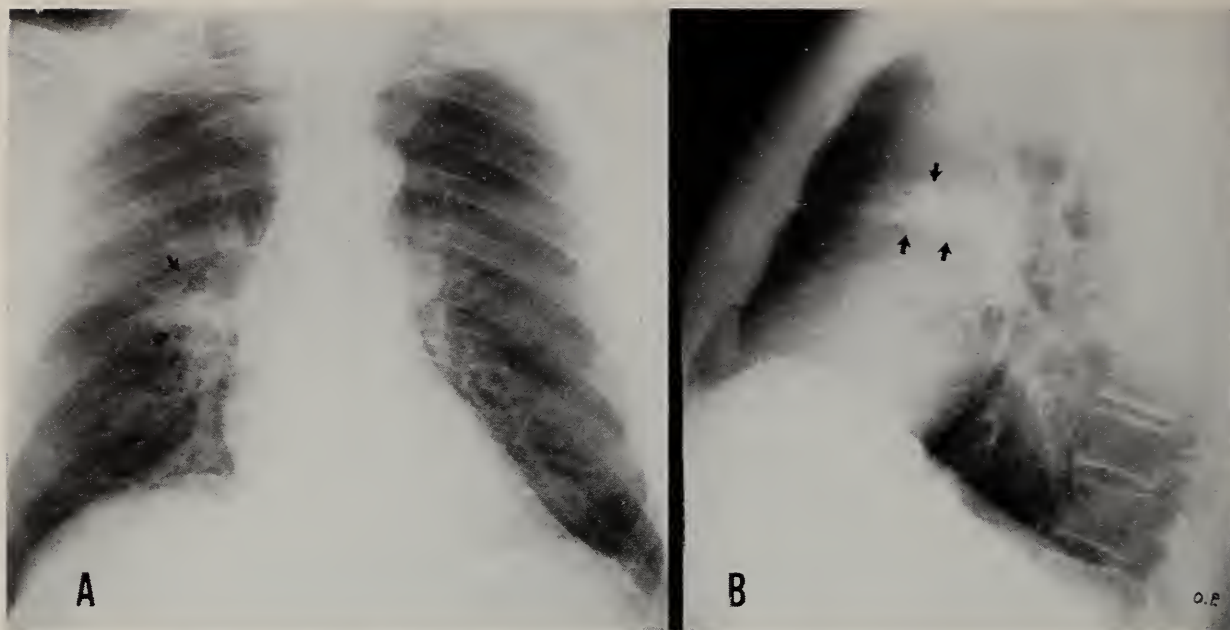


Figure 10.—A 62-year-old man had slight hoarseness and non-productive cough in April 1966. X-ray films elsewhere were reported as showing right lobar pneumonia and effusion. On admission in July 1966 chest x-ray showed increased size and density of the right hilum with infiltrate in the anterior segment of the right upper lobe. Bronchoscopy showed thickening of the right upper lobe orifice and granulation tissue at the right middle lobe orifice. Bronchial and scalene node biopsy, sputa for cytology and fungal growth, and tuberculosis and coccidioidin skin tests negative.

Pre-operative diagnosis was bronchogenic carcinoma. Thoracotomy in August 1966 revealed coccidioidomycosis with demonstration of organisms on tissue section and culture. Repeat skin test with coccidioidin was positive (the pre-operative skin test was presumably inaccurately performed). Complement fixation positive at 1:4 dilution, precipitin negative.

lung involvement is commonly seen as an insignificant linear stranding, but occasionally it is extensive. Bronchiectasis is found in 1 to 2 percent of chronic cases.

Differential Diagnosis

The list of conditions to be considered in differential diagnosis is extensive and includes other fungus diseases⁷ such as blastomycosis, histoplasmosis, actinomycosis, moniliasis, torulosis and other, usually chronic, forms of bronchomycosis (*asperigilius*, *penicillum*, *mucor*) which share with tuberculosis the roentgenographic characteristics expected when there is an organized cellular response to infection. These include adenopathy, persistent parenchymal lesions of many forms (nodular, miliary, massive), and various non-specific infiltrates. Other diseases include bacterial and viral pneumonia, tuberculosis, sarcoidosis, bronchogenic carcinoma, metastatic neoplasm, lymphomas and leukemias. A reliable diagnosis can usually be established by meticulous use of skin and serological tests, sputum culture, or culture and histological study of tissues obtained at biopsy.

Conclusions

The thoracic radiographic findings in coccidioidomycosis fall into a recognizable but non-specific spectrum. Familiarity with the clinical and environmental history as well as the radiographic findings should alert the radiologist to this possible diagnosis. Serological and skin test procedures may then be suggested. The severity of the x-ray findings does not correlate well with incidence of dissemination. The radiologist may alert the clinician to an increased risk of dissemination when the x-ray findings persist or worsen, or if paratracheal adenopathy appears.⁷ There is both clinical and experimental evidence¹⁷ to suggest an increased risk of dissemination during steroid therapy.

In about 75 percent of cases with chronic residual lesions, the lesions will be observed as incidental findings on x-ray examination.¹³ In these cases, surgical proof or recovery of the organisms from sputa or aspirates will be needed for absolute confirmation. Likewise, confirmed pulmonary coccidioidal disease does not exclude the presence of other disease, as evidenced in Birsner's⁴ findings of 24 cases of coccidioidomycosis with co-existing tuberculosis in a total of 500 cases, a 4.8 percent incidence.

Summary

A case of documented acute disseminated coccidioidomycosis is reported. Of interest was the fact that an x-ray film of the chest taken during clinical illness showed no abnormality but films taken three days later showed extensive bilateral nodular infiltrates and mediastinal adenopathy. A review of the roentgenographic manifestations of pulmonary coccidioidomycosis is presented, with attention drawn to the non-specificity of the x-ray findings as well as to the potential for mimicking other diseases.

ACKNOWLEDGEMENT: We express our thanks to Mr. Jules Soute for the photographic reproductions of the radiographs.

REFERENCES

1. Albert, B. L., and Sellers, T. F., Jr.: Coccidioidomycosis from fomites. Report of a case and review of the literature, *Arch. Intern. Med.*, 112:253-261, 1963.
2. Arouson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules, *Arch. Path.*, 34:31-48, 1942.
3. Baum, G. L., and Schwarz, J.: Coccidioidomycosis: A review, *Amer. J. Med., Sci.*, 230:82-97, 1955.
4. Birsner, J. W.: The roentgen aspects of 500 cases of pulmonary coccidioidomycosis, *Amer. J. Roentgen.*, 72:556-573, 1954.
5. Carter, R. A.: The roentgen diagnosis of fungous infections of the lungs with special reference to coccidioidomycosis, *Radiology*, 38:649-659, 1942.
6. Colburn, J. R.: Roentgenological types of pulmonary lesions in primary coccidioidomycosis, *Amer. J. Roentgen.*, 51:1-8, 1944.
7. Colwell, J. A., and Tillman, S. P.: Early recognition and therapy of disseminated coccidioidomycosis, *Amer. J. Med.*, 31:676-691, 1961.
8. Cotton, B. H., and Birsner, J. W.: Surgical treatment of pulmonary coccidioidomycosis, A ten year study, *J. Thorac. Surg.*, 38:435-448, 1959.
9. Dickson, E. C., and Gifford, M. A.: Coccidioides infection (coccidioidomycosis). II. The primary type of infection, *Arch. Intern. Med.*, 62:853-871, 1938.
10. Fiese, M. J.: Coccidioidomycosis, Charles C Thomas, Springfield, Ill., 1958.
11. Forbus, W. D., and Bestbreurtje, A. M.: Coccidioidomycosis: A study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease, *Mil. Surg.*, 99:653-719, 1946.
12. Forsee, J. H., and Perkins, R. B.: Focalized pulmonary coccidioidomycosis, A surgical disease, *JAMA*, 155:1223-1227, 1954.
13. Hensler, N. M., and Cleve, E. A.: Chronic benign residuals of coccidioidomycosis, *Arch. Intern. Med.*, 98:61-70, 1956.
14. Jamison, H. W.: A roentgen study of chronic pulmonary coccidioidomycosis, *Amer. J. Roentgen.*, 55:396-412, 1946.
15. Jamison, H. W., and Carter, R. A.: The roentgen findings in early coccidioidomycosis, *Radiology*, 48:323-332, 1947.
16. Klein, E. W., and Griffin, J. P.: Coccidioidomycosis (Diagnosis outside the Sonoran Zone). The roentgen features of acute multiple pulmonary cavities, *Amer. J. Roentgen.*, 94:653-659, 1965.
17. Lipschultz, B. M., and Liston, H. E.: Steroid induced disseminated coccidioidomycosis. Report of two cases, *Dis. Chest*, 46:355-359, 1964.
18. Melick, D. W.: The surgical treatment of pulmonary coccidioidomycosis with a comprehensive summary of the complications following this type of therapy, *Amer. Rev. Tuberc.*, 77:17-21, 1958.
19. O'Leary, D. J., and Curry, F. J.: Coccidioidomycosis. A review and presentation of 100 consecutively hospitalized patients, *Amer. Rev. Tuberc.*, 73:501-518, 1956.
20. Rakofsky, M., and Knickerbocker, T. W.: Roentgenological manifestations of primary pulmonary coccidioidomycosis, *Amer. J. Roentgen.*, 56:141-155, 1946.
21. Smith, C. E.: Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "Valley Fever"), *Amer. J. Public Health*, 30:600-611, 1940.
22. Smith, C. E.: Diagnosis of pulmonary coccidioid infections, *Calif. Med.*, 75:385-391, 1951.
23. Smith, C. E., Beard, R. R., and Saito, M. T.: Pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation, *Ann. Intern. Med.*, 29:623-655, 1948.
24. Smith, C. E., Saito, M. T., Beard, R. R., Kepp, R. M., Clark, R. W., and Eddie, B. U.: Serological tests in the diagnosis and prognosis of coccidioidomycosis, *Amer. J. Hyg.*, 52:1-21, 1950.
25. Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. G., Beard, R. R., and Saito, M. T.: The use of coccidioidin, *Amer. Rev. Tuberc.*, 57:330-360, 1948.
26. Winn, W. A.: Pulmonary mycoses-coccidioidomycosis and pulmonary cavitation. A study of 92 cases, *Arch. Intern. Med.*, 87:541-550, 1951.
27. Winn, W. A.: Coccidioidomycosis, *J. Chronic. Dis.*, 5:430-444, 1957.
28. Winn, W. A.: Coccidioidomycosis and amphotericin B, *Med. Clin. N. Amer.*, 47:1131-1148, 1963.



The Scope and Responsibility of Medicine

A Forum with a Purpose

To engender discussion of what the scope and responsibility of medicine ought to be in today's society, CALIFORNIA MEDICINE printed in its June issue six essays by authors known to have keen if various interest in the subject.

In presenting the essays the editors expressed hope that they would be the beginning of a forum from which a definition of our profession's responsibilities may be distilled. Readers were invited to take part in a continuation of the forum in succeeding issues. Following are four contributions selected from those received to date. Others will be published in the months ahead.

If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102. Keep your essays short, please.

ROBERT S. LONG, M.D.

*Omaha
President, American Society of Internal Medicine*

DOCTOR SHERMAN MELLINKOFF has made the most important point on this subject in his article in CALIFORNIA MEDICINE for June 1968 [Page 409]. The point is that the terms "physician" and "medicine" are not synonymous. While physicians must be involved in both the scientific and the socio-economic aspects of health care, it is not realistic to expect them as individuals or as organized groups to assume all the responsibility and provide all the leadership for all the socio-economic factors involved in the total health care problem of the nation. Physicians do not and can never have control of all the hundreds of organizations and thousands of persons also directly involved in either patient care or health services. Without control, there can be no expectation of full responsibility.

The primary role of the physician as a professional person should include:

1. Professional *services* to the sick and injured.
2. Professional *teaching* to students and public.
3. Professional *leadership* in community projects directly related to health matters.

4. Professional *guidance* in community projects indirectly related to health matters.
5. Professional *control* of himself as an example in deportment, maintenance of health, social and economic responsibilities.

The scope of "medicine" in the broad definition should include the following:

1. The personal care of the individual patient
 - a. Relieve pain and suffering.
 - b. Prolong life.
 - c. Provide comfort and reassurance.
 - d. Prevent disease and injury.
2. Protection of the Health of the Community
 - a. Environmental—air, water, food, drug, pest control.
 - b. Personal—disease and injury, immunization, information.
 - c. Facilities—hospital, office, home care.
3. Education
 - a. Premedical, Medical, Postgraduate for physicians.
 - b. All paramedical personnel.
 - c. Patients and public in health matters.
4. Research
 - a. Basic—in the biological and biochemical sciences.

- b. Applied—in clinical areas.
- c. In methods of delivery and financing of health care.
- 5. Social Welfare
 - a. Provide medical perspective on social problems such as old age, housing, food, clothing, recreation, education, employment.
 - b. Provide leadership in community projects directly related to health care such as providing hospital and other facilities for the care of the sick, immunization programs, public education in health matters, environmental control measures for the prevention and control of disease and injury.
 - c. Set the example and the standards for the deportment for all good citizens.

Many volumes could be written on the material outlined above and no doubt each heading and sub-heading could be expanded.

While it would be wasteful of time and energy to enter into an endless discussion of semantics, it does seem important at this time for *physicians* to make it unmistakably clear exactly what they can and will do and to place the primary responsibility for the things they cannot do in the health care field where it belongs.

HENRIK L. BLUM, M.D.

*Berkeley
Clinical Professor of Community Health Planning,
University of California, Berkeley,
School of Public Health*

DESPITE THE FOCUS ON broadening the responsibilities of medicine, I find myself concerned with the lack of clarity around the role of medicine (and thus of physicians) in what must be called promoting man's state of well-being. All of the articles presented so far in this exchange tend to focus upon the health professionals' need to look broadly and then do a better and more efficient job *inside* of medical care.

The scope of comprehensive planning for health suggests that what is needed most is a broad look around us to see what can be done *outside* of the traditional medical care field, to work with persons from other sectors of society in determining where the next major blows need to be struck for health. I predict that most of the useful points of attack won't be in the health services. I deplore our tremendous preoccupation with "fixing" man's health deficiencies through health services alone.

Let us grant that health services are one of the major factors in creating a state of well-being. Then, let us look at several other factors that are, at least in aggregate, infinitely more important in determining health status.

One of these factors is environment, in which I include: (a) the physical, such as housing, neighborhood, transport, etc.; (b) the educational; (c) the economic or employment status; and (d) the social. All of these are major determinants of how healthy we are. In the United States today, the degree of poverty and the lack of education, along with the social situations they create, influence more than anything else the likelihood of premature loss of life or health.

In fact, how we respond to nature's warning of ill health and how we use health services are largely functions of these influences. Another major determinant of our health, then, is the sum of our habits and health behavior. These are responses or current reflections of all the environmental influences that have impinged on us. Do we smoke, drink, use drugs unwisely or excessively, undereat or overeat, take preventive precautions, drive safely, etc.? All of these patterns of response or behavior play a major role in determining how long we survive and with what degree of good health.

The last major contributor to human well-being that I

shall mention is genetics, and interventions in this area are indeed carried out primarily in the health sector.

If these things are so, how is it that we in medicine try to put the entire burden on health services to decrease our infant mortality, extend our lives, and improve the quality of living? If we continue in the traditional path of tinkering with the delivery mechanism instead of looking at the whole machine, we in the United States may shortly reach the 100 billion dollars per year mark for health services expenditures and still find ourselves far down the scale in international health comparisons. Health services per se are a "too little" and "too late" approach to overcome the effects of critical deficiencies manifested as excessive or premature morbidity, disability and death which are nowadays more directly contingent upon the other factors described than upon a lack of health services.

I don't want to see medicine trapped in the position of volunteering to correct the significant health deficiencies in this country finally acknowledged in the mid-60's, by recommending expenditures in the wrong sector and then go on to become scapegoats in the mid-70's when fantastically increased expenditures based upon our say-so, have failed to solve major current health problems.

In the practice of medicine, we do an analytic study of each patient's ills, bringing other specialized skills to bear as needed. We prescribe differently for each patient, as called for by our analysis of his systems and how they interrelate. Why can't we pursue the same systems approach so that we can see better where we have to attack problems at the broad community level? Let us contribute our analytic skills to the diagnostic efforts required, to the prognosing and treating, the modifying of health care for the total community when called for. But, let us not blindly volunteer the laying on of health hands when our diagnosis tells us that other interventions are the sole, the earlier, the less expensive, or the more easily attained means of solving health problems. Let us not aggravate a situation in which health services are growing dearer and scarcer by demanding more health services for inappropriate uses which offer lower and lower pay-offs per health dollar spent.

This is a plea to undertake problem analysis before plunging into solutions. If this were to be the order of business, changes in the health delivery system hastily proposed, such as the current promotion of group practice or preventive care, might be made only after it had been determined whether or not such changes will lead to solutions of the problems that need solving most.

WILLIAM D. HOLDEN, M.D.

*Cleveland
Professor and Director, Department of Surgery,
Case Western Reserve University School of Medicine,
and University Hospitals of Cleveland*

SOME OF THE MORE evangelical socialists within the medical profession have presented with considerable ardor criticism of the profession for not only its failure to confront the social ills of a disturbed democracy but indeed its failure to abolish them. This appears to be an exceedingly naive approach to the problems of a complex social structure that extend far beyond the purview, responsibility, and expertise of the medical profession and will almost certainly continue to in the future.

The medical profession has a responsibility for bringing, in the most effective way it can, its capability to the preservation and restoration of the health of the people. The restoration of health is in large measure the responsibility of the medical profession through services provided by individual physicians and through the creation and maintenance of standards of performance of health-related institutions, teaching facilities and programs, and the delivery of care. It is obvious that many related pro-

professional and vocational groups, such as nurses, dietitians, technicians, physical therapists, and others participate in the whole process of delivering medical care. The primary responsibility, however, is with the medical profession. The future scope of medicine will continue to embrace this responsibility but with more attention than is presently given to the role and responsibility of other professional and vocational groups in the health science field.

The preservation of health, however, is quite a different matter and is the responsibility of society as a whole. The problems that bear upon the preservation of health are legion and their solution requires the expertise of many individuals with differing capabilities—the universities, private foundations, and notably governmental agencies. Medicine can be helpful in the solution of these problems by pointing out how they affect the health of individuals and participating in their solution where it has knowledge and capability to bring to bear upon the problems. Medicine is grossly mistaken, however, if it views itself as the white knight that can solve such colossal problems as poverty, restricted education, housing, unemployment, undernutrition, water and air pollution, economic instability, international discord, crime, traffic inadequacies, and many others, all of which play a role in the preservation of national health. The scope of medicine should include its receptivity to participate in the solution of these problems to the extent of its capability. It can participate directly in the preservation of health by providing periodic examinations for segments of society and by conducting immunization programs. It can and should through its individual physicians as citizens participate in discussions and solutions of national social problems. However, the magnitude and complexity of the problems are such that medicine as an organized profession will inevitably have a relatively minor role.

Medicine is poorly prepared to accept many of these responsibilities for the preservation of national health because of its divisiveness and the autonomy with which its many segments function. Clinical medicine is overwhelmingly practiced by specialists and this very likely will be even more apparent in the next decade. The multiple specialty organizations as a group represent the strength and leadership of clinical medicine. The glaring deficit in this arrangement is the almost total lack of cohesion among the specialty societies and the absence of any strong central leadership to function on behalf of medicine as a whole.

Whatever resides in the scope of medicine for the future that pertains to the preservation of health cannot be discharged effectively by medicine unless strong central leadership is provided by medicine itself or unless society through its governmental agencies assumes the total responsibility for providing leadership. The latter alternative would be an obsequious admission of defeat for the private enterprise system.

JURGEN RUESCH, M.D.

*San Francisco
Professor of Psychiatry, University of California,
San Francisco, School of Medicine*

IN OLDEN DAYS the social order was structured around persons, and the physician helped individuals to fight illness to the best of his ability. The doctor in the com-

munity personally knew the patient, and he himself treated the majority of all the ailments that occurred in the family. But the new world has a different outlook. From a patient and disease oriented medicine—identified doctor, identified patient, and diagnosed illness—we have moved to a health oriented medicine—group practice, patient population, and health risk. From the notion of acute disease as an incidental, time-limited, undesirable threat to life and limb, we have arrived at the notion of health as a permanent state of well-being. Inasmuch as the maintenance of healthy conditions requires resources that by far exceed those of the physician, the government has taken on the job of sponsoring the well-being of the citizens in terms of their health, education, and welfare. These aspects of living, which formerly belonged to the private sector of the economy, now have become a public responsibility.

As medicine developed beyond its basic concern with saving lives and managing the aftermath of trauma and disease, it added to its prerogative of treatment the notion of prevention. Modern health practices aim at controlling man in his surroundings, and hence they are both person- and situation-oriented. But change of the internal and external conditions that lead to human suffering requires a vast array of procedures. In addition to periodic medical examinations, immunizations, and treatment of incipient diseases, the maintenance of health for the individual also requires extensive educational campaigns, control of food and drugs and of water and air pollution, prevention of the population explosion, and influence upon the design for housing, transportation, and the like. Concern with mental health of the individual, the family structure, child raising practices, recreation, retirement, and old age is also pertinent in the maintenance of the population's well-being. To carry out these diversified activities, we find biochemists, biophysicists, geneticists, engineers, computer programmers, administrators, behavioral and social scientists, and other professionals working side by side with the physicians in the vast field that is referred to as the health sciences. This is where we stand at the present moment.

Now for a look at the future. If the first developmental stage of medicine was characterized by an emphasis upon organs and organisms, eventually leading to organ repair and other triumphs of modern surgery, the second stage, with its emphasis upon the organism in its natural habitat, led to the spectacular control of communicable and deficiency diseases. Both periods, however, contributed little towards the conquest of chronic diseases and conditions associated with aging and social and physical stress. In the third stage that we are about to enter, some of these problems may be solved, not by emphasizing the existing habitat but by constructing entirely new environments that may require the use of drug additives, the ingestion of synthetic foods, and reliance upon artificial light. The fourth stage, still somewhat in the future, will focus on the prevention of certain diseases by means of genetic control. Modern system approaches, which choose and design the surroundings to fit people, will force a radical reorientation of medical endeavors and a complete overhaul of the curricula in medical, dental, nursing, and pharmacy schools. Students will have to be prepared to work as members of multidisciplinary teams, and subjects such as biophysics, medical economics, population control, environmental design, social engineering, and related topics will have to be introduced. The design and the maintenance of a world in which people can live with self respect in a state of health is the aim of modern medicine.

Board of Medical Examiners

Recent Changes in Laws Relating to Practice in California

JUSTIN J. STEIN, M.D., *Los Angeles*

THE MEDICAL PROFESSION and the State Board of Medical Examiners have joint responsibility for providing the best possible medical care for the citizens of California, for maintaining the highest standards of medical excellence, and for preserving the integrity of the practicing physicians.

The 11 professional members of the board are practicing physicians representing different medical specialties in various parts of the state. Each member is working for the best interests of the public and the medical profession. These physicians are not bureaucrats in any sense of the word and there has been very little political influence exerted in the appointment of board members. The one lay member of the board has also consistently advocated policies which will uphold the standards of medical excellence and he has been most helpful in discussions of matters pertaining to the functions of the board.

The California Medical Association has demonstrated effective leadership in recommending certain changes that have been made in the Business and Professions Code relating to the practice of medicine and surgery in California. In 1963 the CMA House of Delegates adopted resolutions recommending that the State Board of Medical Examiners be given broader authority to discipline physicians who habitually engage in unethical and immoral conduct, those who become professionally incompetent and those with psychiatric disability which interferes with the proper treatment and care of patients. At the 1964 meeting of the House of Delegates two additional resolutions were in-

troduced requesting the CMA in cooperation with the board to determine ways in which to improve the functions and duties of the board. Dr. Carl Anderson was appointed chairman of an ad hoc committee for the purpose.

In addition to the major duties of the board (which are to examine and license eligible applicants and to discipline and rehabilitate physicians who have violated the laws) there is a definite obligation for the members of the board to keep abreast of advances made in medicine, to study new techniques for assessing the professional competence of physicians, to help provide for flexibility in the licensure laws and to maintain a close liaison with professional and paramedical groups.

The important recent changes in the Business and Professions Code relate to mental illness, gross negligence, gross immorality and gross incompetence, and to hospital standards and the establishment of district review committees. These changes are briefly commented upon as follows:

Mental Illness (Article 13.5)

Section 2416. The adjudication of insanity or mental illness, or the voluntary commitment or admission to a state hospital of any licensee for a mental illness shall operate as a suspension of the right to practice of any certificate holder under this chapter, such suspension to continue until restoration to or declaration of sanity or mental competence. The record of adjudication, judgment or order of voluntary commitment is conclusive evidence of such insanity or mental illness, and upon receipt of a certified copy of any such adjudication, judgment, voluntary commitment or order by the board it shall immediately suspend the certificate of the person adjudicated or committed. The board shall not restore such certificate to good

The author is a member and past president of the Board of Medical Examiners, State of California.

From the Department of Radiology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles.

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Reprint requests to: Department of Radiology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles 90024.

standing until it shall receive competent evidence of restoration to or declaration of sanity and until it is satisfied that, with due regard for the public interest, said person's right to practice may be safely reinstated. Before reinstating such person, the board may require the person to pass an oral or written examination, or both, to determine his present fitness to resume his practice.

(Added by Stats. 1965, Ch. 1459.)

Section 2417. If a certificate holder becomes mentally ill to the extent that he requires supervision or restraint or if a certificate holder becomes mentally ill to the extent that he is dangerous to himself or to the person or property of others and is in need of supervision or restraint, the board may take action against him by any one of the following methods:

- (a) Suspending judgment.
- (b) Placing him upon probation.
- (c) Suspending his right to practice for a period not exceeding one year.
- (d) Revoking his certificate.
- (e) Taking such other action in relation to the certificate as the board in its discretion deems proper.

The board shall not restore such certificate to good standing until it shall receive competent evidence of the absence or control of the condition which caused its action and until it is satisfied that with due regard to the public interest the person's right to practice may be safely reinstated.

Before reinstating such a person, the board may require the person to pass an oral or written examination, or both, to determine his present fitness to resume his practice.

(Added by Stats. 1965, Ch. 1459.)

Section 2418. The board may proceed against a certificate holder under either Section 2416 or 2417.

(Added by Stats. 1965, Ch. 1459.)

Section 2419. In setting aside action taken under Section 2416 or under Section 2417, the board may impose terms and conditions to be followed by the certificate holder after his certificate has been reinstated. The authority of the board to impose terms and conditions includes, but is not limited to the following:

- (a) Requiring the certificate holder to obtain additional medical training and to pass an examination upon the completion of the training. The examination may be written or oral, or both, and

may be a practical or clinical examination, or both, at the option of the board.

- (b) Requiring the certificate holder to submit to a complete diagnostic examination by one or more physicians and surgeons appointed by the board. If the board requires the certificate holder to submit to such an examination, the board shall receive and consider any other report of a complete diagnostic examination given by one or more physicians of the certificate holder's choice.

- (c) Restricting or limiting the extent, scope, or type of practice of the certificate holder.

(Added by Stats. 1965, Ch. 1459.)

Gross Negligence: (Section 2361 amended by Stats. 1965, Ch. 1458)

The board shall take action against any holder of a certificate, who is guilty of unprofessional conduct which has been brought to its attention, or whose certificate has been procured by fraud or misrepresentation or issued by mistake.

Unprofessional conduct includes, but is not limited to, the following:

- (a) Violating or attempting to violate, directly or indirectly, or assisting in or abetting the violation of, or conspiring to violate, any provision or term of this chapter.

- (b) Gross negligence.

- (c) Gross incompetence.

- (d) Gross immorality.

- (e) The commission of any act involving moral turpitude, dishonesty, or corruption, whether the act is committed in the course of the individual's activities as a certificate holder, or otherwise or whether the act is a felony or a misdemeanor.

- (f) Any action or conduct which would have warranted the denial of the certificate.

Hospital Standards

Section 2392.5 The regular treatment of or prescribing for patients in a licensed general or specialized hospital having five or more physicians and surgeons on the medical staff which does not have rules established by the board of directors thereof to govern the operation of the hospital, which rules, include, among other provisions, all the following, constitutes unprofessional conduct within the meaning of this chapter:

- (a) Provision for the organization of physicians and surgeons licensed to practice in this state who

are permitted to practice in the hospital into a formal medical staff with appropriate officers and bylaws and with staff appointments on an annual basis.

(b) Provision that membership on the medical staff shall be restricted to physicians and surgeons and other licensed practitioners competent in their respective fields worthy in character and in professional ethics, and in this latter connection the practice of division of fees under any guise whatsoever shall be prohibited and any such division of fees shall be cause for exclusion from the staff.

(c) Provision that the medical staff shall be self-governing with respect to the professional work performed in the hospital; that the medical staff shall meet periodically and review and analyze at regular intervals their clinical experience; and that the medical records of the patients shall be the basis for such review and analysis.

(d) Provision that adequate and accurate medical records be prepared and maintained for all patients.

(Added by Stats. 1965, Ch. 1460.)

Section 2392.6. The regular treatment of or prescribing for patients in a licensed general or specialized hospital having less than five physicians and surgeons on the medical staff, which does not have rules established by the board of directors thereof to govern the operation of the hospital, which rules include, among other provisions, all of the following, constitutes unprofessional conduct within the meaning of this chapter:

(a) Provision that membership on the medical staff shall be restricted to physicians and surgeons and other licensed practitioners competent in their respective fields, worthy in character and in professional ethics, and in this latter connection the practice of division of fees under any guise whatsoever shall be prohibited and any such division of fees shall be cause for exclusion from the staff.

(b) Provision that adequate and accurate medical records be prepared and maintained for all patients.

(Added by Stats. 1965, Ch. 1460.)

District Review Committees (Article 2.3 Added by Stats. 1965, Ch. 1456)

A total of five district review committees were created within the jurisdiction of the Board of Medical Examiners of the State of California. Each committee shall be composed of five persons ap-

pointed by the Governor from among the residents of the district, except as provided in Section 2123.3, who hold valid physician's and surgeon's certificates.

Section 2123.7. Each committee shall hear all matters assigned to it by the board, including, but not limited to, any contested case which is assigned to it by the board.

Section 2123.8. Except as otherwise provided in this article, all hearings which are conducted by a committee shall be conducted in accordance with the provisions of Chapter 5 (commencing with Section 11500), Part 1, Division 3, Title 2 of the Government Code.

If a contested case is heard by a committee, the hearing officer who presided at the hearing shall be present during the committee's consideration of the case and, if requested, shall assist and advise the committee.

Section 2123.9. At the conclusion of any hearing which is conducted by a committee, the committee shall prepare a proposed decision, in such form that it may be adopted by the board as the decision in the case, and shall transmit it to the board.

Section 2124. The board may adopt the proposed decision of a committee in any case in its entirety, reduce the proposed sanction and adopt the balance of the proposed decision, dismiss the case, return the case to the committee or to a hearing officer of the Office of Administrative Procedure for reconsideration, assign the case to any other committee or to a hearing officer of the Office of Administrative Procedure for rehearing, or grant a complete hearing de novo before the board.

Section 2124.1. Except as otherwise provided in this article, any hearing de novo before the board shall be conducted in accordance with the provision of Chapter 5 (commencing with Section 11500, Part 1, Division 3, Title 2 of the Government Code).

Section 2124.2. Any action of the board pursuant to this article is final, except that:

(a) The board may, on its own motion or on petition of any party, within the time and in the manner prescribed in Chapter 5 (commencing with Section 11500), Part 1, Division 3, Title 3, of the Government Code, order a reconsideration of all or any part of a case.

Section 2124.3. The board may adopt, amend, or repeal, in accordance with the provision of

Chapter 4.5 (commencing with Section 11371), Part 1, Division 3, Title 2 of the Government Code, such regulations as may reasonably be necessary to enable it to carry into effect the provisions of this article.

Number of Licensed Physicians

The Board of Medical Examiners has renewed the licenses of more than 53,000 physicians with approximately 34,000 or 64.5 percent residing in California. Reciprocity is given to graduates of all approved medical schools in the 50 states. Citizenship is not required for licensure. Reciprocity is granted without examination to all candidates having a National Board of Medical Examiners Certificate, provided they apply within five years of the date of receipt of their M.D. degree. All physicians who are graduates of medical schools in the United States who have been out of school over five years must take an oral examination in order to obtain a license to practice based upon reciprocity with another state.

State and County Medical Organizations

State or county medical societies do not have the authority to enforce the laws which regulate the profession. Medical societies are established for scientific and educational reasons. Also many physicians do not belong to county or state medical societies and are therefore beyond the authority of those organizations. In California, only about 67 percent of physicians are members of the state medical association.

The county and state medical associations are able to do considerable voluntary reviews and supervision of their physician members. The public can also register complaints against any of the members and such complaints are evaluated by the appropriate committees.

Physicians who are members of good hospitals have their professional activities scrutinized by the appropriate committees. Some physicians do not belong to any hospital staff or organized medical society and therefore are not embraced in the system of self-discipline that guides members of the organized medical profession.

Neither the hospital or medical society can impose legal sanctions against a member and there is no immunity from legal action given to physicians who testify against other physicians. Usually when a physician sues a hospital or other physicians he does so through civil action and for mone-

tary award, alleging loss of income from practice, defamation of character, and the like. When the members of the board as a result of their board duties are involved in litigation, the action at law is usually one that is brought to have the board decision nullified or modified in some manner.

Source of Complaints to the Board

The Board of Medical Examiners receives complaints from the public, patients, law enforcement and state agencies, medical societies and other licentiates of the board. In short, anyone can register a complaint against a licensed physician (Tables 1, 2 and 3).

The complaint should be submitted in writing directly to the Board of Medical Examiners Sacramento Office, and all known facts including names, dates, places and any available records and the names of persons involved should be given.

TABLE 1.—*Complaints Referred for Investigation Relating to Physicians and Surgeons*

Number of Complaints	Origin of Complaints				
	1963	1964	1965	1966	1967
Information from the State					
Bureau of Criminal Investigation and Identification ..	34	43	51	52	85
Law Enforcement agencies ..	93	100	160	124	165
Other Licentiates	19	11	23	21	23
Medical Societies	12	5	8	17	23
Patients	27	20	30	72	74
Reinstatement of Revoked Certificate Modification of Probation	20	40	32	44	53
News Clippings	7	10	5	9	9
Insurance Company	5	3
Anonymous	9	16	26	28	43
Hospital or Pharmacy	7	15	35	36	47
Miscellaneous	14	14	11	33	7
	247	274	381	436	532

TABLE 2.—*Length of Hearings and Number of Cases Heard by District Review Committees*

	1966		1967	
	Duration (Days)	Number of Cases	Duration (Days)	Number of Cases
District Review Committee I	2	1	2	1
District Review Committee II	9	5	4	4
District Review Committee III	2	1	3	3
District Review Committee IV	5	5	5	2
District Review Committee V	4	4	1	1
	22	16	15	11

One case partially heard and continued to 1968.

TABLE 3.—*Delay After Filing of Complaint with Board of Medical Examiners*

	1963	1964	1965	1966	1967
Longest Case—No Action.....	35 months	21 months	22 months	22 months	11 months
Shortest Case—No Action.....	2 days	2 days	11 days	2 days	6 days
Average Case—No Action.....	6 months	5 months	5 months	5 months	3 months
Mode—No Action	3 months	2 months	2 months	2 months	2 months
Shortest time case opened and Accusation Filed	1 month 14 days	2 months	15 days	1 month 14 days	2 months
Longest time case opened and Accusation Filed	49 months	36 months	27 months	22 months	10 months
Shortest time case opened and Sent to Attorney General.....	14 days	1 month	5 days	1 month	1 day
Longest time case opened and Sent to Attorney General.....	48 months	32 months	22 months	21 months	11 months
Average time between opening of Case and sent to Attorney General.....	7½ months	7½ months	6 months	7 months	4½ months
Shortest time between Attorney General and Accusation Filed.....	4 days	5 days	2 days	4 days	5 days
Longest time between Attorney General and Accusation Filed.....	23 months	21 months	23 months	15 months	4 months
Average time between Attorney General and Accusation Filed.....	2½ months	3 months	3 months	2½ months	1½ months

The board requires facts in order to determine if it has jurisdiction in the matter. The information has been kept confidential unless the complainant appears as a witness in the case. It is difficult to know just what the courts will decide in the future regarding the board's records or those of any state agency.

The board needs concrete evidence in order that such evidence would be adequate to substantiate the board's decision should it be appealed to the Superior Court by the respondent.

The majority of the complaints against physicians relate to narcotic law violations, self use of narcotics, excessive use of alcoholic beverages, conviction of a felony or a crime involving moral turpitude, dispensing of dangerous drugs without previous examination of the patient or medical indication for them, negligence, incompetence, commission of acts involving moral turpitude, and false claims for services rendered.

With reference to Table 1 it is noted that medical societies have made few complaints to the board. One would expect that many complaints would be initiated from the medical societies. Also hospital medical staffs could make effective use by having action taken by the board against incompetent physicians and those who violate the provisions of the laws regulating the practice of medicine and surgery.

How Complaints Are Processed

If the information received by the Sacramento office of the Board of Medical Examiners seems to

involve unprofessional conduct, it is sent to the Division of Investigation of the Department of Professional and Vocational Standards with authorization for an investigation to determine if there is evidence to warrant further action. Reports are filed periodically during the investigation and at its completion. The Division of Investigation then asks the board either to close the matter without further action or to send the information to the Attorney General's Office to determine whether an accusation should be filed. If the Attorney General finds cause for action and determines sufficient evidence is available, a formal accusation is prepared and sent to the Sacramento office of the board for filing.

The accusation is served on the licensee by registered mail, and along with it goes a statement advising the licensee as to his rights. Also included is a notice of defense, which should be completed and filed by the licensee in the event he wishes to have a hearing on the allegations in the accusation.

If a notice of defense is filed, a determination is then made as to whether the matter will be heard by the board, by a district review committee or by a hearing officer acting for the board. If the hearing is to be by the board, it is scheduled for the next meeting that the board is to hold in the area in which the licensee resides or the alleged violation occurred. If it is to be assigned to a district review committee, a hearing date is secured and a review committee is assembled to hear the matter. For accusations that are to go

before a hearing officer, the Deputy Attorney General consults the Office of Administrative Procedure and sets the time for hearing.

For matters heard either by the board or by a district review committee, a hearing officer from the Office of Administrative Procedure is assigned to advise as to admissibility of evidence and matters of law. The officer also sits with the board and the district review committee when they are in executive session determining whether the licensee is guilty and, if guilty, the penalty. He does not have a vote in the verdict, serving only in advisory capacity.

If the matter is heard by a district review committee or by a hearing officer sitting alone, a proposed decision is prepared and it must be adopted by the board before it is served on the licensee. If the board does not adopt the proposed decision, there are various provisions of law relating to what further action must be taken.

Funds for the Board

Money to operate the Board of Medical Examiners comes entirely from licensees' payments of reciprocity, examination and registration fees.

When the new legislation authorizing the establishment of five district review committees was enacted, the board doubled the amount of money usually budgeted for investigators, for the services of the Attorney General's staff and for the Office of Administrative Procedures. So far the number of cases to be investigated and to be heard by the District Review Committees has not greatly increased and the board may therefore find itself with a surplus of funds. If the surplus continues, the biennial registration fee for physicians may be reduced.

District Review Committee Experience

The members of the district review committees have been requested to comment upon the value of such committees. The members are unanimous in their comments that it is an excellent educational experience, that the work of the committee

is of definite value to the medical profession and the laity, that the opportunity is provided for prompter hearing of cases, and that the existence of such committees may act as a deterrent to physicians who engage in borderline activities. As the committees are composed of physicians who have had considerable professional experience and broad backgrounds, they can do a great deal toward rehabilitating miscreant physicians so that they can become again useful productive members of society.

It was originally contemplated that the district review committees would be much more active than has been revealed by the record (Table 2), and it is still anticipated that as the experience of the committee members progresses, cases involving gross incompetence, gross negligence, and gross immorality will be referred to them for action. The board must, however, receive the complaints before any action can be taken.

Cases which have been assigned to the district review committees are of the type usually heard by the board or by a hearing officer.

These cases have offered an excellent opportunity for the committee members to become indoctrinated and to gain experience.

It is pointed out that the district review committees do not investigate but that they render decisions on the basis of evidence which is presented directly to them.

There have been many complaints by physicians that there has been too much delay before the board has taken any action. In Table 3 it will be noted that there has been considerable lessening of delay during the past four years and it is hoped that complaints will be more expeditiously handled in the future.

BIBLIOGRAPHY

1. Compilation of Laws Relating to the Practice of Medicine and Surgery, Podiatry, Dispensing Opticians, Physical Therapy and Psychology. Extracted from the Business and Professions Code as in effect 15 Sept. 1965, State of California Department of Professional and Vocational Standards, Sacramento, California.
2. Regan, J. F.: Your License and the Law, The Bulletin of the Los Angeles County Medical Association, Los Angeles, California, 3 Nov., 17 Nov., and 1, Dec. 1966.
3. Anderson, C. E., and Stein, Justin, J.: Problem Areas in Medical Discipline, Cal. Med., 101:384-392, Nov. 1964.

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**California
Medicine**



EDITORIAL

Systemic Manifestations of Malignant Disease

MALIGNANT TUMORS are injurious to the host by local invasive properties (with hemorrhage, infection and loss of function), by metastatic spread to other parts of the body, and by certain systemic manifestations. Increasing attention has been paid to these systemic complications of local neoplasia for several reasons. First, they may represent the initial evidence of the presence of malignant disease, and awareness of their significance may in individual cases lead to earlier diagnosis. Secondly, the systemic complications may represent the major source of disability in a patient and therefore require primary attention in order to prolong life and reduce suffering. Finally, the presence of remote and often mysterious alterations in structure and function raises interesting challenges concerning the biological nature of the neoplastic process.

Elsewhere in this issue of CALIFORNIA MEDICINE there is a discussion of some of the systemic manifestations of hypernephroma, certainly one of the most adroit clinical mimics in its pathogenetic versatility. Perhaps only carcinoma of the lung and thymoma can match hypernephroma in the variety of clinical syndromes produced. The humoral syndromes have been particularly intriguing, such as the excessive production of erythropoietin or parathyroid hormone in carcinoma of the kidney. The kidney is the most important normal source of

erythropoietin; increased production during malignant disease representing loss of rate control.

But why should neoplastic renal tissue produce a highly specific hormonal polypeptide such as parathyroid hormone? Two general theories have occupied the attention of investigators in this area. The first has been called that of "chaotic synthesis," which implies that the neoplastic cell, perhaps in a frenzy of synthetic epilepsy, rather randomly produces a variety of polypeptides and proteins some of which incidentally and unfortunately have hormonal action. There is no direct evidence for this theory and in fact very little evidence that neoplastic cells are capable of synthesizing structurally abnormal proteins. Even the Bence-Jones protein has turned out to be a normal light chain of gamma globulin.

The second theory suggests that normal hormones and other proteins are produced through derepression of the genetic codon. This requires a word of explanation. Perhaps the most important residual problem in cell biology is that of differentiation. Evidence suggests that every cell in the body has the same complement of genetic information in its DNA code, but only a fraction of this information finds expression within the individual cell. The mechanisms by which inappropriate information is repressed during differentiation is not entirely clear, although considerable progress is now being made in investigating this in a number of laboratories. During malignant transformation there may be de-differentiation due to loss of control of code expression. Containing the same genetic information as the parathyroid chief cell, the malignant renal cell is now capable of synthesizing parathyroid hormone. Perhaps it synthesizes albumin or prothrombin or engages in some of the

selective biochemistry of the Betz cell. This would be hard to detect since it is only in the area of hormonal secretion that we have an "endogenous bio-assay."

The syndromes associated with malignant disease are many and varied. They are worthy of careful attention by the physician, the clinical investigator and the biologist alike.

An Illogicity to Be Avoided

SINCE HEALTH IS BECOMING a major goal of this nation, if not of the world, it may be expected that all sorts of efforts and approaches will be made to lessen if not overcome the disparity between expectations and available resources. It is inevitable that full use will be made of whatever statistical data are available concerning needs and resources, and that what is coming to be known as systems analysis will be tried as a means to find more efficient ways of bringing resources to bear upon whatever is determined to be the need. This new technology, augmented (as it is certain to be) by automated data processing and computerization, is full of promise for improved and more efficient health care, but this promise depends for its fulfillment upon a recognition that health is an individual proposition and not something to be handled simply as a matter of statistical probability.

The biological distribution curve gives expression to this essential point. It is well recognized that no two specimens of a biological species are ever exactly alike. If any characteristic such as weight or height is measured, a distribution curve may be constructed by plotting numbers of specimens against their various heights, weights or whatever. From this curve such things as averages, means, modes and probabilities may be calculated and much useful information may be derived about the sample as a whole. But, most significantly, none of these calculations can predict where upon the curve any particular specimen of the sample will be found, except in terms of statistical probability.

An important illogicity occurs whenever it is assumed that the characteristics of any individual specimen are actually the same as the average, or the mean, or the mode or even a statistical prob-

ability which may be derived from the distribution curve. The fact is that each human being is genetically unique and also unique in his life experience, and because of this there is a reasonable chance that his ailments will be either unique or uniquely expressed. This biologic and sociologic reality is well known to physicians and patients and accounts for much of their opposition to systematization in medical care.

Illogicity of this sort must not be allowed to creep into planning for health services. As costs increase and as the extent of the disparities between expectations and resources becomes more accurately assessed by modern statistical technology, there is apprehension that the illogical step of equating the human recipient of health care services with the statistical probability will be taken by systems-oriented planners who either do not recognize or underrate the uniqueness of human beings. The danger is that the needs of a health care delivery system for economic efficiency somehow may be permitted to take precedence over the needs of the patients which the system was presumably designed to serve. The aim to be achieved is somehow to blend (1) the needs for economy and efficiency, (2) the capabilities of modern data processing and systems analysis, and (3) the needs for individualization of health care services which derive from the biologic and sociologic uniqueness of each person.

The expectations for health, in the nation and the world, can be realized only if this most important illogicity in planning for health care services is recognized and avoided.

A Treatment For Viral Infections?

FOR ALMOST A quarter of a century, physicians have been able to treat many bacterial infection effectively with antimicrobial drugs. This stands in sharp contrast to our inability to influence many human viral diseases which constitute a large proportion of patients' acute complaints. The resulting frustration has, at times, led to the unwarranted and undesirable use of antibacterial drugs for the "prevention" of hypothetical complications of viral infections.

The discovery of interferon in 1957 by Isaacs and Lindemann* provided a ray of hope. Here was a potent inhibitor of the replication of many different viruses and one which was non-toxic for host cells. If such material could be produced on a large scale, it might be the long hoped-for universal antiviral drug. Regrettably, the early hopes and expectations were not fulfilled. The pronounced host-specific effect of interferon limited its potential application and the small yield of interferon in laboratory systems posed apparently insuperable difficulties for commercial production. For these and other reasons, *exogenous* interferon has been largely abandoned as a potential antiviral drug.

On the other hand, it was discovered that a wide variety of substances was capable of inducing the formation or release of *endogenous* interferon made by the host's own cells. Some inducers were relatively simple molecules, some were non-antigenic and could therefore be given repeatedly, many were non-toxic. This provided a powerful new stimulus for the investigation of the physical, chemical, and biological properties of interferon and its potential in therapy. Elsewhere in this journal, Dr. T. Merigan, a leading investigator of interferon, presents a detailed and critical appraisal of some recent developments in this area.

It seems probable that endogenous interferon, stimulated by virus infection, plays an important role in limiting viral proliferation in an infected tissue and thus limiting injury to tissue. Interferon appears to be an important mechanism in bringing viral disease to an end. By contrast, preformed antibody (for example, after vaccination or post infection) may prevent infection by a given specific virus, but plays little part once an infection has established itself. It is tempting to believe that stimulation of endogenous interferon by non-toxic and non-immunogenic inducers could be employed in many viral infections to abort or prevent disease. In view of the broad spectrum of viruses suppressed by interferon, it would not even be necessary to formulate a specific viral diagnosis before employing this agent—at times an appealing thought. These possibilities are so attractive that large pharmaceutical manufacturers are intensively pursuing research in these directions. In the immediate future, however, such a universal antiviral compound is not in sight for the practitioner. Most clinical trials with exogenous interferon have given

marginal results and some of the more dramatic claims for the clinical efficacy of interferon-inducers (especially from the U.S.S.R.) require confirmation.

For the molecular biologist, interferon offers an exciting challenge, permitting glimpses into the cell's mechanisms which transmit information and control synthesis of viral components. It appears at present that interferon acts upon ribosomes where active protein synthesis takes place. It is reasonable to predict that knowledge about the molecular biology of interferon will accumulate faster than its practical application in medicine. Nonetheless, the dream of a universal antiviral treatment may come true through progress in this field of investigation.

Medicine and Human Behavior

AS THIS IS WRITTEN another assassin's bullet has snuffed out the life of another American of courage and outspoken conviction. Perhaps the assassin was demented, perhaps an opportunist, or perhaps a person of courage with his own peculiar conviction. An anguished nation is asking itself why, what is wrong, and how can violence be curbed, whatever its cause. There is something awful about the present capability of a minority of one human being to affect the lives of so many, whether his finger is on the trigger of a gun or on a button which could unleash a nuclear holocaust.

This is not the place to explore the extent to which a minority, whether an individual or a group, whether advantaged or disadvantaged, whether black, white or some other color or race, should have the power or the right to impose its will upon a civilized nation, upon the civilized world, or even upon a simple majority of whatever group. Nor is this the place to examine the concept of the protest—that theory which says that if I believe I know what is right then I have a responsibility to bring about what I believe to be right even if I have to violate a law to do so, and that what I am doing is so right and so important that it doesn't matter if I have to deny others the same rights and privileges I claim for myself in order to get it done. This concept not only underlies the illegal protest, whether violent or non-violent, but it is also the blind conviction of extremists of both the political right and left.

*Isaacs, A., and Lindemann, J.: Virus Interference, I. Interferon. Proc. Roy. Soc. (London), 147:258-267, 1957.

These are, however, matters of human behavior, and medicine therefore is appropriately concerned. Behavior is an important factor in health maintenance, in seeking health care when it is needed, and in many other aspects of well-being or being well. It is important in the causation of disease, injury and emotional disturbance whether in individuals, groups of individuals or even crowds. And surely an understanding of human behavior is important when there is a human finger pressing on an individual trigger or a global push button.

But biological and medical science knows all too little of these phenomena. Certainly genes have something to do with it. Nutrition has something to do with it. Life's experience, the "conditioning" process, culturally accepted behavior, one's own "thing," the comfort of conformity, and personal conviction are each important. For the animal kingdom, behavior is recognized as a biological phenomenon and its nature is properly studied within the framework of the life sciences. It has been said that in humanity life has become aware of itself, but certainly this late evolutionary awareness has not changed the basically biological nature of human beings and human behavior.

It is suggested that the time has now come, both in the nation and in the world, for the principles and technology of biology and medicine to be focused more directly upon human behavior. It is suggested that a biological approach now be introduced into the behavioral, social and political sciences and that these scholarly disciplines begin to take more cognizance of the biological nature of the subject matter with which they deal. As knowl-

edge of the basic biological nature of human behavior and human society accumulates it will become possible to apply many of the principles of medical practice to problems of health and disorder in human behavior, not only in individual persons, but in civilized society, and its many segments in the community, in the nation and throughout the world. Only when and as this is done will the human achievement of awareness of life be matched by the science and techniques necessary to understand and promote civilized behavior among human beings in a civilized world.

A New Director of Public Health

Just at press time we have the pleasure of expressing our well-wishes to Louis F. Saylor, M.D., M.P.H., upon his appointment as California's Director of Public Health.

Dr. Saylor, who has been with the Department of Public Health for the past seven years as assistant chief of the Division of Research, comes to a post that traditionally has been served by men of outstanding ability and we believe he will extend that tradition.

With our congratulations to him goes our earnest offer of cooperation and assistance.



California Medical Association

Council Highlights

Highlights of the Actions of the California Medical Association 544th Council Meeting, May 3 to 4, 1968, Sacramento

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA Headquarters office.

Prepayment for Government Health Care programs was reaffirmed when the Council adopted a position paper which summarized previous positions of Council and the House of Delegates. The statement, which suggests a mechanism similar to that used by many private groups for purchasing group health insurance, also says, "After a year's actual experience under the Medi-Cal program, it now appears feasible that a prepayment program for providing indigent care is in fact practical."

Guidelines for Medi-Cal Review Committees as prepared by CMA Legal Counsel Howard Hasard were approved by Council for use by component societies. These guidelines, intended to minimize the chances of reversal of a review committee's recommendations, either by the State Health and Welfare Agency or the courts, provide for procedural due process, which means that the physician involved has prior notice, an opportunity to be heard, and a hearing before the committee.

California Medical Education and Research Foundation (CMERF) recommendations as approved by Council included the following actions:

- Approval of Part I of "A Survey of Continuing Medical Education for Physicians" for distribution to component societies and others.
- Approval of recipients of the California Phy-

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The *Workmen's Compensation Guide for Physicians* (revised, 1968) is now available to physicians throughout California. It has been prepared by the California Medical Association's Committee on Occupational Health and it is updated and in a new format.

Copies may be obtained by writing to:
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693 Sutter Street
San Francisco, California 94102



Guidelines for Determination of Disputed Questions of Medical Fact in Workmen's Compensation Cases. Guidelines based on a study of problems in cardiac cases have been prepared with the assistance of the Medical Advisory Committee of the Division of Industrial Accidents. These guidelines have been approved by the California Medical Association's Committee on Cardiovascular Diseases. Single copies are available to physicians from the office of:

Roy J. Bell
Administrative Director
Division of Industrial Accidents
455 Golden Gate Avenue
San Francisco, California 94102

sicians' Merit Scholarships and acceptance of the CMERF financial report.

- Approval of CMERF participation in funding a second "Planning and Goals Conference" in Continuing Education.

Scientific Board's Committee on Continuing Medical Education was authorized to retain an educational consultant to evaluate the educational effectiveness of the 1969 West Coast Counties Regional Postgraduate Institute.

A critique of the President's Health Message to Congress dated March 4, 1968 was accepted for dissemination to the profession and the public. The critique, which was prepared by the CMA Bureau of Research and Planning, pointed out that the Health Message contained misuse and inappropriate use of data, leading to further misconceptions about increases in physicians' fees.

Three subcommittees established by the Communications Commission were approved by Council, namely: Subcommittee on Commission Roles and Objectives, Subcommittee on Component County Medical Society Officers Conference, and a Subcommittee on Commission Budget.

Commendation of the *San Francisco Examiner* for its contribution of the 20-week full page "Health Forum" series, prepared in cooperation with CMA, was approved in resolution form for presentation to the *Examiner*.

Workmen's Compensation Guide for Physicians was approved for appropriate distribution to the profession. The purpose of the Guide, as presented by the CMA Commission on Public Agencies Chairman, is to inform physicians of their role and responsibilities when concerned with cases covered under the Workmen's Compensation law. The Guide was prepared by the Committee on Occupational Health.

CMA Committee on Organizational Review and Planning proposal establishing priorities was approved by Council for CMA study and action in response to the Report of the National Advisory Commission on Health Manpower. The priorities are: (1) physician manpower in California, (2) organization and delivery of health care services, and (3) peer review.

California Volunteers for Political Action received Council endorsement to expand the CALPAC Board to 45 members including representatives from each of California's 38 congressional districts, the Woman's Auxiliary to CMA and the Medical Executives Conference.

Physicians in Private Group Practice

Recent Data, California and United States

A Socio-Economic Report of the
Bureau of Research and Planning,
California Medical Association

ALMOST 20 PERCENT of all physicians in private practice in California belonged to group practices at the end of July 1967.

Of the 4,730 physicians in 598 groups, slightly over two-thirds were in multi-specialty groups, and the remainder in single-specialty arrangements

Sources: American Medical Association Department of Health Care Services: Listing of Group Practices in the United States, 2nd Edition, December 1967; and Group Practice: Journal of the American Association of Medical Clinics, 17 February 1968.

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco 94102.

consisting of three or more physicians. Most single-specialty groups are relatively small, while multi-specialty groups are often much larger.

Of the 598 group practices, 381 with 1,279 physicians had either three or four members. However, 22 large group practices of 25 or more individuals accounted for 1,774 physicians. Among multi-specialty groups only, more than half of all physicians were in groups of 25 or more individuals.

Counties with the largest number of physicians in group practices were the following: Los Angeles, Santa Clara, Alameda, San Francisco and San Diego. There were 20 counties, all of which were non-metropolitan, in which no group practices existed.

Counties with the greatest proportion of physicians in groups, as compared with all physicians in private practice were: Yolo, Yuba, Solano, Santa Clara, Tuolumne and Stanislaus—all with 35 percent or more.

Tables 1 and 2 of this report classify information according to county, number of single- and multi-specialty groups, and numbers and percentages of physicians involved. The data are derived from a recent publication of the American Medical Association, together with revisions made by the Bureau of Research and Planning.

Table 3 contains some comparative data for the United States and for California. The national statistics are for the year earlier and are taken from a different source; however, some general conclusions can be made from them. They are the following:

1. The proportion of *groups* in California compared with the United States is approximately the same as the proportion of *physicians* in California compared with the number in the U.S. (just under 14 percent of each—a figure not shown in the table);

2. The percent of physicians in private practice who are members of groups is considerably higher in California than it is nationally, 19.9 percent vs. 16.5 percent;

3. The average size of group practices is larger in California—7.9 vs. 6.6 physicians per group (these figures are *mean* averages; median group size is four physicians in California and, although it could not be determined for the total United States, is probably about the same), and

4. Considerably more physicians are in large size groups in California (37.5 percent vs. 28.0 percent in groups of over 25 members) and in multi-specialty groups (67.6 percent vs. 57.3 percent).

TABLE 1.—*Number and Percent of Single- and Multi-Specialty Groups and Participating Physicians in California, by Number of Full-Time Physicians in Group Practice as of July 1967*

Number of Full-time Physicians in Group Practice	<i>All Groups</i>		<i>Single-Specialty</i>		<i>Multi-Specialty</i>		Percent of all Physicians in Multi- Specialty
	Number of Groups	Number of Physicians	Number of Groups	Number of Physicians	Number of Groups	Number of Physicians	
3	245	735	200	600	45	135	18.4
4	136	544	98	392	38	152	27.9
5	67	335	42	210	25	125	37.3
6	28	168	14	84	14	84	50.0
7	16	112	5	35	11	77	68.8
8	19	152	10	80	9	72	47.4
9	13	117	4	36	9	81	69.2
10	12	120	4	40	8	80	66.7
11-14	15	182	2	24	13	158	86.8
15-19	13	220	0	0	13	220	100.0
20-24	12	271	0	0	12	271	100.0
25 and more	22	1,774	1	31	21	1,743	98.3
Total	598	4,730	380	1,532	218	3,198	67.6

TABLE 2.—Number and Percent of Physicians in Group Practice, by County* as of July 1967

County	Number of Physicians in Group Practices			Number of All Physi- cians in Private Practice	Percent of Physicians in Group Practice
	Single Specialty	Multi- Specialty	Total		
Alameda	81	231	312	1,463	21.3
Butte	7	5	12	125	9.6
Contra Costa	9	127	136	540	25.2
El Dorado	5	3	8	34	23.5
Fresno	33	17	50	386	13.0
Humboldt	9	..	9	92	9.8
Kern	5	47	52	260	20.0
Kings	3	..	3	41	7.3
Los Angeles	534	1,215	1,749	9,474	18.5
Marin	30	49	79	317	24.9
Mendocino	8	8	55	14.5
Merced	5	..	5	64	7.8
Monterey	15	22	37	238	15.5
Napa	3	20	23	98	23.5
Nevada	4	4	23	17.4
Orange	77	55	132	1,347	9.8
Placer	13	7	20	67	29.9
Riverside	26	41	67	421	15.9
Sacramento	51	88	139	691	20.1
San Bernardino	15	134	149	556	26.8
San Diego	153	105	258	1,335	19.3
San Francisco	120	177	297	1,825	16.3
San Joaquin	21	3	24	263	9.1
San Luis Obispo	28	28	107	26.2
San Mateo	59	122	181	672	26.9
Santa Barbara	12	62	74	341	21.7
Santa Clara	135	406	541	1,281	42.2
Santa Cruz	9	24	33	152	21.7
Shasta	12	..	12	91	13.2
Solano	10	42	52	114	45.6
Sonoma	15	17	32	233	13.7
Stanislaus	15	58	73	199	36.7
Sutter	3	..	3	24	12.5
Tulare	7	20	27	134	20.1
Tuolumne	6	6	16	37.5
Ventura	22	14	36	276	13.0
Yolo	18	23	41	75	54.7
Yuba	18	18	38	47.4
Total State	1,532	3,198	4,730	23,722	19.9

*The following counties have no group practices: Alpine, Amador, Calaveras, Colusa, Del Norte, Glenn, Imperial, Inyo, Lake, Lassen, Madera, Mariposa, Modoc, Mono, Plumas, San Benito, Sierra, Siskiyou, Tehama and Trinity.

TABLE 3.—Comparative Statistics about Group Practice, United States and California

Data	United States* (1966)	California (1967)
Number of groups	4,287	598
Number of physicians in group practice	28,420	4,730
Percent of all private practitioners in group practice	16.5%	19.9%
Mean number of physicians per group	6.6	7.9
Percent of physicians in groups consisting of more than 25 physicians	28.0%	37.5%
Percent of physicians in group practices who are in multi-specialty groups	57.3%	67.6%

*Source: Group Practice: *Journal of the American Association of Medical Clinics*, 17: February 1968.

ACTIONS OF THE HOUSE OF DELEGATES

San Francisco, March 23 to 27, 1968

NOTE: *The following report of the transactions of the House of Delegates of the California Medical Association is selected and abridged. A complete transcript of all proceedings is on file in the Association office in San Francisco and available for the inspection of all members.*

REFERENCE COMMITTEES

COMMITTEES APPOINTED by Speaker William F. Quinn at the first meeting of the House of Delegates Saturday evening, 23 March, were as follows:

Committee on Credentials: A. J. Murrieta, Jr., Los Angeles, Chairman; A through L component societies: George S. Buehler, Whittier; George C. Andersen, Hermosa Beach; Paul D. Yates, Hermosa Beach; Walter Brignoli, St. Helena and Emmett Rixford, San Francisco.

M through Z component societies: Stanley A. Skillicorn, San Jose; David T. Clary, Santa Rosa; Gordon Bowen, Lynwood; A. B. Sirbu, San Francisco and Robert Hippen, San Diego.

Reference Committee 1: (This committee reviews the reports of the officers, the Council, the commissions and standing and special committees.) John A. Bullis, Los Angeles, Chairman; Gerald Ingle, Corning; Harold Messenger, San Diego; Harvey E. Starr, Los Angeles and Edgar Wayburn, San Francisco.

Reference Committee 2: (This committee on finance reviews the reports of the secretary, executive director and studies and makes recommendations to the House of Delegates on the budget submitted by the Council and on the amount of dues for the ensuing year.) Chester Tancredi, San Diego, Chairman; Ralph M. Milliken, Los Angeles; A. E. Berman, Sacramento; George K. Herzog, Jr., San Francisco and Walter P. Ellerbeck, Los Angeles.

Reference Committee 3: (This committee considers new and miscellaneous business.) Robert T. Hood, Jr., Van Nuys, Chairman; Harold Miles, Santa Barbara; Frederick Ackerman, Pleasant Hill; James Martin, Sacramento and Thomas El-mendorf, Willows.

Reference Committee 3A: (To consider business of Committee 3 when the volume becomes too great for one committee to handle.) Leonard Asher, Beverly Hills, Chairman; M. M. Haskell, Long Beach; Vincent Carroll, Laguna Beach; Glenn A. Pope, Sacramento and Henry J. Rulfo, Ventura.

Reference Committee 3B: (This committee also is a supplement to 3 and 3A.) Chester Herrod, San Francisco, Chairman; Edward Liston, Palo Alto; Wallace Gerrie, Newport Beach; Bernard Axelrod, Los Angeles and Harry E. Hill, Northridge.

Reference Committee 4: (This committee considers amendments to the Constitution and By-laws.) Robert L. Day, Bakersfield, Chairman; Mason Hohl, Beverly Hills; Ralph Beasom, Los Angeles; Clarence T. Halburg, Redlands and John V. Pollack, Los Angeles.

California Blue Shield (CPS) Reference Committee: (This committee considers new and miscellaneous business pertaining to California Blue Shield (California Physicians' Service).) Herbert Holden, San Leandro, Chairman; J. E. Vaughan, Bakersfield; H. H. Stone, Riverside; Stanley Tru-man, Oakland and Wilbur Bailey, Los Angeles.

PRESENTATION OF FIFTY-YEAR AWARDS

Pins commemorative of 50 years of membership in the California Medical Association were presented to the following physicians: Los Angeles: S. M. Alter, William H. Daniel and William J. McKenna; San Francisco: Hans Klusmann and Charles P. Mathe; San Luis Obispo: A. H. Wilmar; Santa Clara: Thomas Blanchard.

RECOGNITION AND AWARDS

John G. Morrison was presented a plaque for his two years of dedicated service to the CMA as President and President-Elect. Malcolm C. Todd was presented the President's gavel.

Plaques for outstanding contributions were presented to Mr. Eldon Geisert as outgoing chairman of the Medical Executives' Conference.

Past Presidents were recognized as were official representatives of allied health professions.

Dr. Dwight L. Wilbur, President-Elect of AMA, was recognized and given a set of engraved bookends for his outstanding contributions to the CMA.

Mrs. William R. Flood, President of the Woman's Auxiliary, was recognized and gave a summary of auxiliary activities.

Dr. Edwin H. Lennette was awarded a plaque in recognition of his efforts in virus research.

Dr. Albert G. Miller was awarded a silver gavel as retiring chairman of the Council.

ELECTIONS

OFFICERS (One-Year Terms)

Malcolm C. Todd, Long Beach, was installed as President. Albert G. Miller, San Mateo, was elected President-Elect. William F. Quinn, Los Angeles, was re-elected Speaker of the House of Delegates. Joseph F. Boyle, Los Angeles, was re-elected Vice Speaker of the House of Delegates.

COUNCIL (Three-Year Terms)

Second District—Frank C. Melone, Ontario; Fourth District—Office No. 1—Maurice H. Haskell, Long Beach; Fourth District—Office No. 4—Lewis T. Bullock, Los Angeles; Fourth District—Office No. 7—George C. Andersen, Hermosa Beach; Seventh District—Office No. 2—John T. Saily, San Mateo; Eighth District—Office No. 1

—Albert G. Clark; Eleventh District—Thomas N. Elmendorf, Willows.

COUNCIL (Two-Year Term)

Fourth District — Office No. 9 — Frank A. Rogers, Whittier.

AMA DELEGATION

Unexpired Terms Starting March 26, 1968

Delegate, Leon P. Fox (unexpired term of Burt Davis).

Alternate, Richard S. Wilbur (unexpired term of Leon P. Fox).

Two-Year Terms Starting January 1, 1969

DELEGATES

John G. Morrison, San Leandro; William F. Quinn, Los Angeles; Robert C. Combs, Irvine; Homer C. Pheasant, Los Angeles; Alfred J. Murrieta, Los Angeles; Leon P. Fox, San Jose; Arlo A. Morrison, Ventura; James E. Feldmayer, Exeter; O. W. Wheeler, Riverside; Malcolm C. Todd, Long Beach; J. E. Vaughan, Bakersfield; Carl E. Anderson, Santa Rosa.

ALTERNATES

Frederick Ackerman, Pleasant Hill (alternate to John G. Morrison); Dudley M. Cobb, Los Angeles (alternate to William F. Quinn); Emmett Rixford, San Francisco (alternate to Robert C. Combs); James C. MacLaggan, San Diego (alternate to Homer C. Pheasant); Harold Kay, Oakland (alternate to Alfred J. Murrieta); Richard S. Wilbur, Palo Alto (alternate to Leon P. Fox); Henry Brown, San Mateo (alternate to Arlo A. Morrison); Charles Grayson, Sacramento (alternate to James E. Feldmayer); Wilbur Bailey, Los Angeles (alternate to O. W. Wheeler); Neil C. Hamel, Encino (alternate to Malcolm C. Todd); Joseph P. O'Connor, Pasadena (alternate to J. E. Vaughan); Jean F. Crum, Downey (alternate to Carl E. Anderson).

BOARD OF TRUSTEES OF THE CALIFORNIA PHYSICIANS' SERVICE (Three-Year Terms)

Richard F. Altman, M.D., Newport Beach; Burt L. Davis, M.D., Palo Alto; Donald R. Fitch, M.D., Glendale; Bert L. Halter, M.D., San Francisco; Mr. Donald S. Bell, San Francisco.

REFERENCE COMMITTEE RECOMMENDATIONS

Reference Committees are encouraged to comment on any activity of the California Medical Association that comes to their attention. If these observations or recommendations are not directed toward a specific resolution, constitution or bylaw amendment, they are recorded in this section.

REFERENCE COMMITTEE NO. 1

REPORTS

It is recommended that:

1. The appointment of this Committee should be soon after Annual Session therefore allowing meetings with the staff during the year and to review CMA reports.

2. CMA Annual Reports should show the budget, accomplishments and projected goals of each Commission and Committee.

3. Prior to the annual meeting, a listing of the disposition and follow-through for each resolution should be made available to the delegates.

4. The Speaker of the House of Delegates assign resolutions to Reference Committees 3, 3a and 3b on the basis of subject matter in order that attendance at these meetings may be facilitated.

5. Anyone contemplating the submission of a new resolution should first contact the CMA office for computer "Data Text" information available on all previous resolutions. It is hoped that this will facilitate the writing of new resolutions and may eliminate yearly duplications, thereby reduc-

ing the number of resolutions considered by the House.

ACTION: Adopted.

Referred to: The Speaker of the House.

REFERENCE COMMITTEE NO. 2

FINANCE

1. The Committee recommends that the contribution to the American Medical Education Research Foundation be cut in half from \$110,000 to \$55,000 and be phased out entirely in the 1969 to 1970 Budget.

2. The Committee recommends that an appropriation of \$2,000 be budgeted as an appropriate endorsement and support of the Tumor Tissue Registry.

3. The Committee recommends that funds spent in support of the Medical Library of the Los Angeles County Medical Association not be classified as a contribution but be budgeted as a specific expenditure to the L.A.C.M.A. Library under the budget of the Scientific Board, as done with the Tumor Tissue Registry.

4. The Committee recommends that the dues for the calendar year beginning 1 January 1969 be continued at \$90 per active member.

ACTION: Adopted.

Referred to: Finance Committee.

5. The Committee urgently recommends that the Council appoint a Committee to encourage voluntary individual support of medical education.

ACTION: Adopted.

Referred to: Committee on Continuing Education.

ACTION ON RESOLUTIONS

ONE HUNDRED FOURTEEN RESOLUTIONS came before the 1968 House of Delegates. Each was numbered and assigned to a Reference Committee for consideration and recommendation.

Reference Committees have the option of recommending a resolution for adoption or rejection, for adoption as amended or substituted, or for no action.

Resolutions shown here are in the form in which the House of Delegates approved them for adoption or for referral to the Council or to specified commissions or committees. Where a resolution was not adopted, that report is made here but the language of the resolution is not shown. Copies are available in the CMA office on request.

Each resolution is shown by number and subject and the name and status of each author is recorded.

The action reported at the foot of each resolution was taken by the House of Delegates, March 26 and 27. The referrals were made by the Council at its meeting, May 3 and 4.

1 1 1

SIDNEY J. SHIPMAN, M.D.

Resolution No. 1-68

Committee 3

Introduced by: The Council

WHEREAS, Sidney J. Shipman, M.D., has had an unusually distinguished career of service to medicine over the past forty-seven years; and

WHEREAS, he has served the California Medical Association with ability and dedication as Councilor, Chairman of the Council, Delegate and President, as well as on numerous committees; and

WHEREAS, Doctor Shipman has made outstanding contributions through the San Francisco Medical Society, serving as its President in 1942; and

WHEREAS, his leadership has extended to numerous other areas, including service as the President of the California Tuberculosis Association and the American Tuberculosis Association and as a member of the State Board of Medical Examiners; and

WHEREAS, the Council, by unanimous vote, has requested that the House of Delegates confer "Honorary Membership" in the Association on Doctor Shipman as specified in Chapter II, Section 4(b) of the Bylaws; now, therefore, be it

Resolved: That this House of Delegates elect Sidney J. Shipman, M.D., an Honorary Member of the California Medical Association.

ACTION: Adopted.

SALE OF CIGARETTES IN HOSPITALS

Resolution No. 2-68

Committee 3

Introduced by: Walter F. Carpenter, M.D.

Representing: San Diego County

Resolved: That the physicians of this state endorse and support efforts being made to discontinue the sale of cigarettes within hospitals and recommends to the various hospital medical executive staffs that they work toward the end of discontinuing cigarette sales in their respective hospitals and commends those efforts which have already been made in this regard.

ACTION: Adopted as amended.

Referred to: Commission on Hospital Affairs.

1 1 1

PHYSICIAN-OWNED HOSPITALS

Resolution No. 3-68

Committee 3B

Introduced by: Walter P. Ellerbeck, M.D.

Representing: Los Angeles County Medical Association

Resolved: That this House of Delegates directs the Council to explore with the California Hospital Association the problem of possible conflict of interest as it relates to optimal care in all hospitals, and that a progress report be made to the 1969 meeting of this House.

ACTION: Above substitute resolution adopted.

Referred to: Commission on Hospital Affairs.

1 1 1

RADIATION THERAPY BENEFITS

Resolution No. 4-68

Committee 3

Introduced by: San Mateo County

WHEREAS, certain providers of health care benefits, notably Blue Cross of Northern California, provide radiation therapy benefits only "in lieu of surgery"; and

WHEREAS, radiation therapy may be used either as the sole method of treatment or to complement or supplement surgery and frequently cannot be strictly defined as "in lieu of surgery"; and

WHEREAS, these carriers have used this terminology to withhold benefits from those who rightfully expected coverage for these benefits; and

WHEREAS, this terminology is medically unsound and outmoded and prone to different inter-

pretation in specific instances; now, therefore, be it

Resolved: That this House of Delegates directs the Council of the CMA to inform health insurance carriers and prepaid health plans, by appropriate means, that limitation of liability for radiation therapy benefits by the use of this or similar terminology is medically unsound and unjustified and would be prejudicial to the best interest of their beneficiaries; and be it further

Resolved: That the Insurance Commissioner of the State of California be apprised of the intent of this resolution and be requested to prohibit the use of this limitation of liability in the State of California.

ACTION: Adopted.

Referred to: Commission on Medical Services.

1 1 1

DRUG ABUSE

Resolution No. 5-68

Committee 3

Introduced by: San Mateo County

WHEREAS, drug abuse shall be defined as the intemperate, unauthorized, or illegal self-administration of chemical substances for their mind-altering effect. Such chemical substances shall include, among others, both prescribed and illicitly disseminated drugs of stimulant, sedative, hallucinogenic and narcotic properties—not excluding ethyl alcohol; and

WHEREAS, drug abuse has become a social problem of national importance, far exceeding the capability of a local community to investigate, or control; and

WHEREAS, numerous unrelated lay groups, agencies, quasi-official and official organizations are actively concerned about and involved with the problems provoked by drug abuse; and

WHEREAS, information concerning these drugs is being disseminated indiscriminately without regard to authenticity or source of such information; now, therefore, be it

Resolved: That the California Medical Association shall establish an Interagency Council on Drug Abuse; and be it further

Resolved: That the California Medical Association shall introduce a similar resolution to the delegation of the American Medical Association in order to create such a Council on a National level.

ACTION: Adopted as amended.

Referred to: AMA Delegation and Sub-Committee on Dangerous Drugs for planning.

PROFESSIONAL CORPORATIONS

Resolution No. 6-68

Committee 3

Introduced by: San Mateo County

Resolved: That the California Medical Association exert all legislative efforts to secure passage of legislation to permit formation of professional corporations.

ACTION: Adopted.

Referred to: Committee on Legislation.

1 1 1

DISABILITY AND/OR ILLNESS INSURANCE FOR VOLUNTEER PHYSICIANS SERVING IN VIETNAM

Resolution No. 7-68

Committee 3

Introduced by: Walter Carpenter, M.D.

Representing: San Diego County

WHEREAS, "Project Vietnam" is sponsored by and encouraged by the American Medical Association; and

WHEREAS, the California Medical Association concurs in the encouragement of participation of its members; and

WHEREAS, many individual physicians desire to participate in this program of care for Vietnam civilians; and

WHEREAS, the AMA, CMA and county medical societies' group disability insurance programs will not cover injuries and/or illness incurred in a war zone; now, therefore, be it

Resolved: That the California Medical Association instruct the carrier of its group disability program to arrange immediate coverage for physician volunteers; and be it further

Resolved: That component county medical societies be urged to take similar action with their insurance carriers; and be it further

Resolved: That the California Delegation to the AMA be instructed to introduce a similar resolution at the 1968 annual session in San Francisco in June.

ACTION: Adopted.

Referred to: Commission on Professional Welfare; AMA Delegation; Medical Executives Conference; County Society Presidents.

1 1 1

CONSULTATION WITH LOCAL SOCIETY COMMITTEES

Resolution No. 8-68

Committee CPS

Introduced by: Warren J. Boyer, M.D.

Representing: Yuba-Sutter-Colusa Medical Society

WHEREAS, the California Physicians' Service (California Blue Shield) is the fiscal agent for

Medicare and Medi-Cal programs as well as underwriting agent for a large segment of private prepaid health coverage; and

WHEREAS, Blue Shield has been directed by the State of California to pay the "reasonable" fee of physicians who submit claims on the Medi-Cal program, such "reasonable" fee being determined not to exceed the 60th percentile in local areas as of 1 January 1967; and

WHEREAS, such fee determinations have been arbitrarily set by the State agency without conference with local societies and, further, fail to reflect adjustments which are made of necessity due to increased service and operating costs; and

WHEREAS, continued substandard fees are, in effect, a penalty on private, self sustaining patients already overburdened with subsidies; and

WHEREAS, the State of California and the United States Government, through their respective programs, feel that recipients are entitled to quality medical care, and should be expected to pay no more, but certainly no less, than the standard fee for such care; now, therefore, be it

Resolved: That the House of Delegates of the California Medical Association instruct the California Physicians' Service to consult with established committees of local societies before determining what is a "reasonable" fee for an area; and be it further

Resolved: That they instruct CPS to have such consultation with local committees before decisions are made by a regional or statewide review committee as to arbitrary adjustments of submitted claims without explanation; and be it further

Resolved: That CPS be instructed to investigate and adopt, at the earliest possible time, a mechanism to consider individual claims, with local committee consultation, of a higher fee than that established when this increased claim reflects increased operating and service costs of the concerned physician.

ACTION: Above substitute resolution adopted.

Referred to: Blue Shield Board of Trustees.

1 1 1

INTERIM PAYMENTS

Resolution No. 9-68

Committee CPS

Introduced by: Warren J. Boyer, M.D.

Representing: Yuba-Sutter-Colusa Medical Society

ACTION: No action was taken on this resolution.

ANNUAL MEETING DATES

Resolution No. 10-68

Committee 3

Introduced by: The Council

WHEREAS, the 1960 House of Delegates established the meeting dates of the Annual Session to be held between 15 March and 15 April each year; and

WHEREAS, the competition for outstanding speakers is extremely keen; and

WHEREAS, the competition for adequate hotel space increases as mid-year approaches; now, therefore, be it

Resolved: That the California Medical Association establish the dates of its Annual Meeting to be held between 1 February and 15 March of each year; and be it further

Resolved: That the component medical societies in California be urged to adjust elections and other administrative processes so that earlier scheduling of the Annual Meeting will not create hardships on them or the CMA; and be it further

Resolved: That the intent of this resolution become effective two years after adoption, thereby allowing for the necessary changes in the bylaws and constitutions of component medical societies to be effected.

ACTION: Adopted.

1 1 1

CALIFORNIA PHYSICIANS' SERVICE

Resolution No. 11-68

Committee CPS

Introduced by: E. Kenneth Smith, M.D.

Representing: Humboldt-Del Norte Medical Society

WHEREAS, the California Physicians' Service is primarily an organization operated by the physicians of California for the *people* of California; and

WHEREAS, despite years of service of high order and repute, the California Physicians' Service *has recently had problems in communication with its members*; now, therefore, be it

Resolved: That the California Medical Association through its Officers and Council shall constantly remind the California Physicians' Service that it is vital that they maintain intelligent communication with the physicians they service, avoid secrecy as to the source and programming of criteria used in making their computerized decisions, and establish a comprehensive cross-filing system to allow a ready access to details for prompt replies to enquiries.

ACTION: Adopted as amended.

Referred to: Blue Shield Board of Trustees.

ENVIRONMENTAL QUALITY

Resolution No. 12-68

Committee 3

Introduced by: San Francisco Delegation

WHEREAS, population growth, with heightened population density, rapid advances in technology, increasing urbanization, and changes in living patterns for many of our citizens all have effects on the environment of the United States; and

WHEREAS, the California Medical Association believes in the highest attainable environmental quality, including healthful housing, community noise control, accident prevention, adequate and diversified places of recreation, open space, and control of the adverse effects of crowding; now, therefore, be it

Resolved: That the California Medical Association recognizes the present future necessity of high environmental quality as a major public health concern and urges that responsible government agencies be strengthened in order to develop and provide the technology for defining, measuring and monitoring aspects of environmental quality; and be it further

Resolved: That this resolution be introduced into the House of Delegates of the American Medical Association at its next meeting.

ACTION: Adopted as amended.

Referred to: Committee on Environmental Health; Commission on Community Health Services; AMA Delegation.

1 1 1

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES CERTIFICATE

Resolution No. 13-68

Committee 3

Introduced by: San Francisco Delegation

WHEREAS, the Council on Medical Education of the AMA requires a certificate from the Educational Council for Foreign Medical Graduates (E.C.F.M.G.) for all foreign interns and residents serving in approved internships and residencies in the United States; and

WHEREAS, the California Board of Medical Examiners requires a special written examination before permitting graduates of foreign medical schools to accept appointments as interns or residents in California hospitals; and

WHEREAS, the Council on Medical Education will not accept the written examination of the California Board of Medical Examiners in lieu of the E.C.F.M.G. certificate; now, therefore, be it

Resolved: That the California Medical Association urge the California Board of Medical Examiners to require an E.C.F.M.G. certificate of

foreign medical graduates as qualification for examination; and be it further

Resolved: That the Board of Medical Examiners inform all applicants for examination of the requirement that foreign medical graduates must have an E.C.F.M.G. certificate to be eligible for an approved internship or residency in this state.

ACTION: Referred to Council.

Referred to: Division of Government Relations.

1 1 1

HOSPITAL BOARDS

Resolution No. 14-68

Committee 3B

Introduced by: San Francisco Delegation

WHEREAS, statements in the Health Manpower Commission's report to the President indicate hospitals will be playing a more and more active role in the delivery of health care; and

WHEREAS, the principle of broader representation on hospital governing boards has been endorsed by the CMA and AMA through their recommendations that physicians serve on such boards; and

WHEREAS, most hospitals receive support from a wide spectrum of agencies, by federal, state and local government, voluntary groups, private individuals, organized medicine and physicians themselves; now, therefore, be it

Resolved: That this House not only endorse its prior action but recommend broader representation of the community as a whole on hospital governing boards; and be it further

Resolved: That the CMA, through its Council, communicate with the California Hospital Conference on any necessary changes in The Guiding Principles and seek a joint conference at which this subject may be fully discussed and a joint understanding reached, with a report within six months.

ACTION: Adopted.

Referred to: Commission on Hospital Affairs.

1 1 1

HOSPITAL COSTS

Resolution No. 15-68

Committee 3B

Introduced by: San Francisco Delegation

ACTION: Resolution withdrawn.

1 1 1

MEDICAL EXECUTIVE TRAINING

Resolution No. 16-68

Committee 3

Introduced by: San Francisco Delegation

WHEREAS, the problems of county medical societies have become more numerous and complex

because of government, insurance and labor involvement in health care; and

WHEREAS, the position of Executive Secretary of a county medical society is a highly specialized occupation requiring considerable knowledge and ability; and

WHEREAS, to date there has been no organized plan to train future county medical society executive secretaries; now, therefore, be it

Resolved: That the California Medical Association through its Council explore the feasibility of a medical executive training program in the various major portions of the state.

ACTION: *Adopted.*

Referred to: Medical Executives Conference for study and report back to Council.

1 1 1

OBITUARY NOTICES

Resolution No. 17-68

Committee 3

Introduced by: San Francisco Delegation

WHEREAS, inclusion of the cause of death in the obituary columns of the *Journal of the American Medical Association* and *California Medicine* sometimes can cause embarrassment and additional sorrow to the survivors; now, therefore, be it

Resolved: That the California Medical Association delegation to the American Medical Association requests that the American Medical Association review its policy of listing cause of death in the obituary columns of the *Journal of the American Medical Association*, and be it further

Resolved: That the California Medical Association review its policy of listing cause of death in the obituary columns of *California Medicine*.

ACTION: *Adopted as amended.*

Referred to: Committee on CALIFORNIA MEDICINE; AMA Delegation.

1 1 1

AIR POLLUTION

Resolution No. 18-68

Committee 3

Introduced by: Santa Clara County Delegation

WHEREAS, air pollution is increasing despite efforts to control it; and

WHEREAS, Federal and State laws and regulations now in effect will, at best, maintain the present unsatisfactory conditions; and

WHEREAS, physicians are seeing more patients with diseases attributable to the irritating and dangerous effects of air pollution; and

WHEREAS, it is found necessary to advise some

patients to move away because of man-made air pollution; and

WHEREAS, vehicular air pollution, now the major source in California, is subject to control only by the State and Federal governments; and

WHEREAS, the costs of illness associated with air pollution justify extensive expenditures for its control; now, therefore, be it

Resolved: That it shall be the policy of the California Medical Association to support vigorously all rational efforts for the control of air pollution, to request that the California Legislature and the Federal Congress enact legislation which will promptly curb vehicular air pollution by the enforcement of methods already known to be effective, and to urge the support of studies and the enactment of laws which will assure a healthful air supply in the future; and be it further

Resolved: That the intent of this resolution be introduced into the next meeting of the House of Delegates of the AMA.

ACTION: *Adopted as amended.*

Referred to: Committee on Legislation; Committee on Environmental Health Services; AMA Delegation.

1 1 1

IMPROVE SOCIETY'S ABILITY TO SELF-DISCIPLINE

Resolution No. 19-68

Committee 3B

Introduced by: Santa Clara County Delegation

WHEREAS, the State Board of Medical Examiners may presently discipline physicians for some types of criminal behavior, gross incompetence, gross neglect or gross immorality; and

WHEREAS, the State Board of Medical Examiners is unable to take action in cases of unprofessional but non-criminal conduct by physicians; and

WHEREAS, County Medical Societies can only expel a member by cumbersome and legally hazardous procedure; and

WHEREAS, expulsion means little to the unethical physicians; now, therefore, be it

Resolved: That an ad hoc committee of the CMA be appointed to evaluate the means of providing effective professional discipline by component societies and to study the medical aspects of the Business & Professional Code; and be it further

Resolved: That appropriate recommendations be made prior to the next meeting of this House of Delegates.

ACTION: *Above substitute resolution adopted.*

Referred to: Commission on Professional Welfare.

COMMENDATION OF CALIFORNIA BLUE SHIELD

Resolution No. 20-68

Committee CPS

Introduced by: Joseph W. Telford, M.D.

Representing: San Diego Delegation

WHEREAS, this House of Delegates has passed several policy statements on the desirability of reimbursing physicians on the basis of usual and customary fees as the most equitable method of payment for services; and

WHEREAS, California Blue Shield, our CMA-sponsored organization, and insurance carriers, have been repeatedly requested to apply the usual and customary concept; and

WHEREAS, California Blue Shield, responding to the desires of this House of Delegates, has aggressively sold, to groups and individuals, new programs which include usual and customary fee payments; and

WHEREAS, this marketing effort has resulted in now having approximately fifty percent of Blue Shield subscriber members on usual and customary fees, as of 1967; now, therefore, be it

Resolved: That this House of Delegates express its appreciation to the Board of Trustees and management of Blue Shield for its outstanding record in new sales and the upgrading of plans to include payment to physicians of usual and customary fees; and be it further

Resolved: That county medical societies, their membership, and California Blue Shield continue to cooperate in every possible way to encourage major subscriber groups and others to adopt the usual and customary method of payment for physicians' services.

ACTION: Adopted.

Referred to: Blue Shield Board of Trustees; Officers of component medical societies.

1 1 1

STATE BUDGETARY CUTS IN MENTAL HEALTH SERVICES

Resolution No. 21-68

Committee 3

Introduced by: Leon P. Fox, M.D.

Representing: Santa Clara County Medical Society

WHEREAS, the 1967 cutback in the budgetary funds for the State Department of Mental Hygiene has cancelled important treatment programs and impaired the overall effective function of staff personnel throughout the State; and

WHEREAS, the quantity and morale of the personnel rendering mental health care has been significantly lowered; and

WHEREAS, this "economical" effort of the State Administration has evidenced a deterioration and backward step in medical progress in health care and a resulting costly overall waste that California can ill afford; now, therefore, be it

Resolved: That the California Medical Association emphatically state that it decries the costly results of previous budget cutting for all health services including those of the Department of Mental Hygiene; and be it further

Resolved: That the California Medical Association make every available effort to appeal to the State Administration and Legislature to appropriate adequate funds to restore and upgrade the mental and other health programs in California to acceptable standards.

ACTION: Referred to Council for further study.

Referred to: Commission on Public Agencies for study and report back to Council.

1 1 1

MEDICAL TECHNOLOGY SCHOOLS

Resolution No. 22-68

Committee 3B

Introduced by: Leon P. Fox, M.D.

Representing: Santa Clara County Medical Society

WHEREAS, there now exists a serious shortage of well trained medical technologists; and

WHEREAS, because of this shortage, all qualified institutions should be encouraged to offer training in medical technology; and

WHEREAS, a requirement in the Essentials for Accredited Schools of Medical Technology to require facilities for enrollment of ten or more students will effectively prevent many well qualified institutions from offering approved training; and

WHEREAS, there are many more effective ways to insure that unqualified schools are not approved, such as most importantly an effective individual inspection program; and

WHEREAS, the California Association of AMA Approved Schools of Medical Technology has formally protested changes in the essentials which would eliminate schools on basis of size; now, therefore, be it

Resolved: That the California Medical Association go on record as approving the stand of the California Association of AMA Approved Schools of Medical Technology and make this known to the authoritative American Association of Clinical Pathologists; and be it further

Resolved: That the CMA delegates to the AMA propose a similar resolution to the AMA House of Delegates.

ACTION: Adopted as amended.

*Referred to: Committee on Allied Health Professions;
AMA Delegation.*

1 1 1

NATIONAL STUDY COMMITTEE ON ORGAN TRANSPLANTS

Resolution No. 23-68

Committee 3B

Introduced by: Leon P. Fox, M.D.

Representing: Santa Clara County Medical Society

WHEREAS, the outstanding research in organ transplantation has entered the era of clinical applicability; and

WHEREAS, the tireless investigators and clinicians in this field face an increasing number of challenging problems in religious, moral, ethical and legal as well as medical areas which need definition and clarification; and

WHEREAS, these problems could interfere with progress in this new field of medical science; and

WHEREAS, it is more appropriate for the medical profession to take leadership in solving these problems than others; now, therefore, be it

Resolved: That the delegates from CMA to AMA be directed to introduce appropriate resolutions to the AMA House of Delegates instigating the appointment of a national blue ribbon ad hoc committee including leaders in religion, law and medical science who are knowledgeable in the field of organ transplantation, to study these problems and develop possible guidelines which would be useful to the clinicians.

ACTION: Adopted.

Referred to: AMA Delegation.

1 1 1

PROGRAMS FOR SCIENTIFIC SESSION

Resolution No. 24-68

Committee 3

Introduced by: James J. McCort, M.D.

Representing: Santa Clara County Medical Society

WHEREAS, the meetings of the Scientific Sections of the California Medical Association have in the past not been well attended by the members; and

WHEREAS, the Scientific Sections of the CMA have been separate from the specialty organizations at the State level; and

WHEREAS, the 1967 Conference of Medical Specialty Representatives held at the Hilton Inn 7 October 1967 recommended that the Scientific Sections of CMA be merged with the Specialty Societies at the State level; now, therefore, be it

Resolved: That the CMA Scientific Board make every effort to have the various Scientific Sections interest their respective State Specialty Societies

in having combined meetings at the Annual Session of the CMA.

ACTION: Adopted.

Referred to: Scientific Board.

1 1 1

SUBSIDIZING MEDICAL GROUPS

Resolution No. 25-68

Committee 3A

Introduced by: Howard Lindsey, M.D.

Representing: San Mateo County Medical Society

WHEREAS, the federal government is actively spending our taxes to promote and even subsidize group medical practice; and

WHEREAS, the federal government is not equally promoting and subsidizing the individual or solo-type practice of medicine; and

WHEREAS, this puts the individual practitioner of medicine and especially the physician attempting to enter the solo practice of medicine at a distinct disadvantage; now, therefore, be it

Resolved: That the California Medical Association go on record as opposing this discriminatory practice; and be it further

Resolved: That this resolution be presented to the American Medical Association for appropriate action.

ACTION: Adopted.

Referred to: AMA Delegation.

1 1 1

ALLOWED CHARGES

Resolution No. 26-68

Committee 3A

Introduced by: Howard Lindsey, M.D.

Representing: San Mateo County Medical Society

WHEREAS, the Explanation of Benefits form contains title headings such as "Allowed Charges" and "Charges Not Allowed"; and

WHEREAS, such so-called explanatory terms not only do not accurately describe the basis for payments made to, or on behalf of, recipients, but may imply criticism of the physicians' charges; now, therefore, be it

Resolved: That the Delegation to the American Medical Association request the Board of Trustees to attempt to effect such a change in the terminology of Medicare Explanation of Benefits form through the liaison mechanism to the Social Security Administration which is currently operant.

ACTION: Above substitute resolution adopted.

Referred to: AMA Delegation.

CERTAINTY OF COVERAGE

Resolution No. 27-68

Committee 3A

Introduced by: Howard Lindsey, M.D.

Representing: San Mateo County Medical Society

WHEREAS, many insurance and other medical care programs today are stressing first dollar coverage of limited medical care programs; and

WHEREAS, the patient is always concerned as to whether a certain illness or condition may or may not be covered; and

WHEREAS, the patient's fear that he will not be covered and actual lack of coverage of an illness is far more real and disastrous to the patient than lack of first dollar coverage; now, therefore, be it

Resolved: That the California Medical Association actively stress in all its deliberations and discussions concerning medical care programs with the public, government, insurance companies and other groups, the paramount importance of certainty of coverage.

ACTION: *Referred to Council for further referral to Commission on Medical Services.*

Referred to: Commission on Medical Services.

1 1 1

MEDICAL UTILIZATION REVIEW

Resolution No. 28-68

Committee 3A

Introduced by: Harry E. Hill, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, county medical societies have repeatedly offered their services to self-discipline suspected overutilization practices under the Medi-Cal program; and

WHEREAS, California Blue Shield has vigorously pursued cases of suspected overutilization with, and at the direction of, the county medical society review committees concerned; and

WHEREAS, several physicians and providers of services have been recommended for suspension from the Medi-Cal program in response to this joint effort; now, therefore, be it

Resolved: That the California Medical Association urge the Office of Health Care Services to act expeditiously in the administrative procedures to suspend physicians and providers of services from the Medi-Cal program upon the recommendation of the County Medical Society Review Committee and the California Blue Shield; and be it further

Resolved: That each county medical society in California and California Blue Shield continue their joint efforts, to the fullest extent possible, in case findings and review of suspected overutilization cases in order to improve the quality of medi-

cal care and correct case of overutilization of services; and be it further

Resolved: That this resolution be sent to members of the California Legislature and the Executive Branch of the State Government.

ACTION: *Adopted.*

Referred to: Division of Government Relations to notify Legislature and Office of Health Care Services.

1 1 1

UNJUSTIFIED MEDICAL LITIGATION CASES

Resolution No. 29-68

Committee 3B

Introduced by: M. A. Schmutz, M.D.

ACTION: *Not adopted.*

1 1 1

COMMENDATION FOR DR. JAMES YANT

Resolution No. 30-68

Committee 3

Introduced by: 11th District Delegation

WHEREAS, Dr. James Yant has served the CMA, the Eleventh District and the Sacramento Society for Medical Improvement for many years in an outstanding manner as Councilor, Delegate and in numerous committee capacities; and

WHEREAS, Dr. Yant has indicated his retirement as district councilor; now, therefore, be it

Resolved: That the House of Delegates of the California Medical Association join with the Eleventh District and the Sacramento Society for Medical Improvement in expressing its sincere appreciation and in bestowing its commendation to Dr. Yant for his outstanding representation and leadership.

ACTION: *Adopted.*

1 1 1

MULTIPHASIC SCREENING PROGRAMS

Resolution No. 31-68

Committee 3B

Introduced by: Glenn A. Pope, M.D.

WHEREAS, it appears that some form of multiphasic screening may be extensively tested in the examination of large numbers of individuals; and

WHEREAS, such programs can only be successful with proper planning, supervision and adequate follow-up; and

WHEREAS, such programs have recently been tried and are being proposed where the above criteria have not been fulfilled; and

WHEREAS, such planning and evaluation can best be done within existing medical facilities; now, therefore, be it

Resolved: That the California Medical Association request any organization contemplating such

a program to establish liaison for the purposes of consultation and assistance.

ACTION: Above substitute resolution adopted.

Referred to: Commission on Community Health Services.

1 1 1

RADIATION THERAPY

Resolution No. 32-68

Committee 3

Introduced by: Charles Grayson, M.D.

ACTION: No action was taken on this resolution.

1 1 1

CMA TELEVISION PROGRAM

Resolution No. 33-68

Committee 3B

Introduced by: Lewis H. Lambert, M.D.

ACTION: No action was taken on this resolution.

1 1 1

SAN FRANCISCO CENTENNIAL COMMENDATION

Resolution No. 34-68

Committee 3

Introduced by: 11th District

WHEREAS, the San Francisco Medical Society is enjoying its Centennial year; and

WHEREAS, the San Francisco Medical Society has served the California Medical Association and the State of California well for many years by supplying outstanding, dedicated physicians to serve in vital and important positions; now, therefore, be it

Resolved: That the House of Delegates join with the Sacramento Society for Medical Improvement and the 11th CMA District in commending the San Francisco Medical Society on its 100th anniversary; and be it further

Resolved: A suitable scroll be prepared to honor this occasion.

ACTION: Adopted.

Referred to: Division of Professional and Public Relations.

1 1 1

MEDI-CAL ELIGIBILITY CERTIFICATION

Resolution No. 35-68

Committee CPS

Introduced by: Abe E. Berman, M.D.

WHEREAS, the determination of eligibility for Medi-Cal services has been a major factor causing frequent delay in processing of claims for payment; and

WHEREAS, the State of California and California Blue Shield as fiscal intermediary have been studying various methods of eligibility certification, in-

cluding a pilot program with a multi-card system in San Bernardino County; now, therefore, be it

Resolved: That the California Medical Association commend all such efforts to solve this complex problem and urge that all parties give major priority to improving the mechanism of eligibility certification for Medi-Cal services.

ACTION: Adopted.

Referred to: Blue Shield Board of Trustees; Division of Government Relations.

1 1 1

SACRAMENTO CENTENNIAL COMMENDATION

Resolution No. 36-68

Committee 3

Introduced by: Thomas Elmendorf, M.D.

WHEREAS, on 17 March 1968 the Sacramento Society for Medical Improvement, known as the Sacramento County Medical Society, achieved the distinction of 100 years of continuous successful and distinguished service; and

WHEREAS, the Sacramento Society for Medical Improvement has been a strong and leading constituent of the California Medical Association through these hundred years; and

WHEREAS, throughout the century, the Sacramento Society has furnished many distinguished officers to the California Medical Association House of Delegates, the Council and its committees; and

WHEREAS, the Sacramento Society for Medical Improvement has also furnished invaluable services to the California Physicians' Service and the Public Health League; now, therefore, be it

Resolved: That the House of Delegates and the Council concurring, extend to the Sacramento Society for Medical Improvement its heartiest congratulations and sincerest wishes for continued service; and be it further

Resolved: That a suitable scroll be inscribed and forwarded to this ancient and honorable member society.

ACTION: Adopted.

Referred to: Division of Professional and Public Relations.

1 1 1

MEDICAL DATA PROCESSING

Resolution No. 37-68

Committee 3A

Introduced by: Franklin Murphy, M.D.

WHEREAS, the explosive growth of data processing capabilities has wrought profound changes in hospitals, medical insurance and government; and

WHEREAS, the physicians of California need fur-

ther representation of their interests in this field; now, therefore, be it

Resolved: That a committee be established by the Council of the California Medical Association to represent the physicians of California in the broad field of automation and data processing, including the processing of claims for physicians' services, to the end that the needs of physicians will be properly recognized in the programming of this rapidly developing facet of medicine and medical economics.

ACTION: *Referred to Council for further referral to Bureau of Research and Planning.*

Referred to: Bureau of Research and Planning for study and report back to Council.

1 1 1

MEDI-CAL RESOLUTION

Resolution No. 38-68 Committee 3A

Introduced by: Edward J. Wiater, M.D.

Representing: Long Beach Delegation

ACTION: *No action was taken on this resolution.*

1 1 1

NARCOTICS AND DANGEROUS DRUGS

Resolution No. 39-68 Committee 3

Introduced by: Thomas Kiddie, M.D.

Representing: Long Beach Delegation

WHEREAS, the abuse of narcotics and dangerous drugs is a serious and increasing problem in our society today; and

WHEREAS, our young persons are most vulnerable to this threat, and by the same token most susceptible to education underlying the extreme dangers involved; now, therefore, be it

Resolved: That the California Medical Association increase its activities in disseminating information as to the true dangers of narcotics and dangerous drugs; and be it further

Resolved: That the California Medical Association, at its earliest convenience, establish workshops and/or other educational programs to bring the latest and most authentic data on the physiologic and pathologic effects of these dangerous substances to our members, so that they in turn can disseminate this information to our youth, to parents, to teachers, and all others interested in the well-being of our society; and be it further

Resolved: That the California Medical Association assist those medical societies which do not presently have committees on narcotics and dangerous drugs to establish them.

ACTION: *Adopted as amended.*

Referred to: Sub-Committee on Dangerous Drugs.

STANDARD INSURANCE BILLING FORM

Resolution No. 40-68

Committee 3A

Introduced by: Edward J. Wiater, M.D.

Representing: Long Beach Delegation

WHEREAS, with the advent of governmentally regulated programs of health care, an ever increasing demand of "paper work" on the part of physicians has resulted; and

WHEREAS, the physician's responsibility primarily should be centered on the patient care, not on "paper care"; and

WHEREAS, fiscal intermediaries for Medi-Cal, Medicare and Champus programs, as well as Blue Shield, Blue Cross and other insurance carriers have demanded completion of their individualized insurance forms for reimbursement of physicians' services; and

WHEREAS, standardized insurance forms have been developed in the past to meet the needs of insurance companies; and

WHEREAS, automated copying machines provide quick, clear and simplified means of providing billing information and thus should eliminate the copying of this information on insurance forms; now, therefore, be it

Resolved: That the California Medical Association study, develop, implement and authorize the creation of a standardized simplified form for billing of Medi-Cal, Medicare, Champus, as well as other insurance billing for physicians' services; and be it further

Resolved: That such an insurance form provide for the rendering of necessary billing information by automated copying machines; and be it further

Resolved: That the insurance companies concerned be advised of this effort and be invited to cooperate and to help in the development of such a standardized simplified form; and be it further

Resolved: That the staff of the California Medical Association exert its efforts to the promotion and acceptance of this form by patients, insurance companies and doctors.

ACTION: *Referred to the Council for further referral to the Commission on Medical Services.*

Referred to: Commission on Medical Services.

1 1 1

STUDY AND SUPPORT OF PRECEPTORSHIPS

Resolution No. 41-68

Committee 3B

Introduced by: James W. Goettle, M.D.

Representing: Tulare County Delegation

WHEREAS, the use of preceptorships to acquaint medical students with some of the facts of the pri-

vate practice of medicine before they decide upon their main interest is an old and proven system; and

WHEREAS, in California the establishment and funding of such preceptorships has not been systematic and has not been fostered by CMA; now, therefore, be it

Resolved: That the subject of preceptorships be studied by the Board of CMERF and if possible funds awarded to support them.

ACTION: *Adopted.*

Referred to: California Medical Education and Research Foundation.

1 1 1

QUALITY AND MAINSTREAM MEDICAL CARE

Resolution No. 42-68

Committee 3A

Introduced by: Charles D. Kranzdorf, M.D.

WHEREAS, the art and science of medicine in its highest form in the twentieth century takes the position that man is a totality whose illnesses can only be fully understood when the entire psychobiologic unit is apprehended at one time; and

WHEREAS, the practice of medicine requires the free and unfettered application of any and all knowledge appropriate to the diagnosis and treatment of disease as it naturally occurs; and

WHEREAS, artificially compartmentalized views of human illness render disservice to the patient and demean the physician who seeks to practice his profession honorably through the exercise of his best judgment without regard to the source of compensation for his services; and

WHEREAS, to take a contrary position is to invoke a double standard of medicine predicated upon the wealth of the patient rather than the needs of the patient; and

WHEREAS, the indigent of the State of California are entitled to mainstream medical care; now, therefore, be it

Resolved: That

1. The California Medical Association affirms the position that each patient should be afforded diagnosis and treatment as seems appropriate to his needs regardless of the presence or absence of any governmental or non-governmental agency asserting fiscal responsibility.

2. The California Medical Association resists, in all ways possible, incursions upon the free exercise of medical judgment.

3. The California Medical Association opposes any and all attempts to discriminate against any segment of the indigent medical population on the basis of diagnosis, or against any segment of the

medical profession, on the basis of medical, psychiatric, surgical or other specialties practiced.

ACTION: *Adopted as amended.*

Referred to: Division of Government Relations.

1 1 1

LOCAL DETERMINATION IN PL 749 PROJECTS

Resolution No. 43-68

Committee 3A

Introduced by: William G. Donald, M.D.

Representing: Alameda-Contra Costa Medical Association

ACTION: *See Resolution No. 93-68 with which this resolution was combined.*

Referred to: ad hoc Task Force on Public Law 89-749; AMA Delegation.

1 1 1

PODIATRY

Resolution No. 44-68

Committee 3B

Introduced by: Harold J. Eisenberg, M.D.

Representing: Alameda-Contra Costa Medical Association

WHEREAS, the medical profession has determined that it is in the best interest of the public that surgeons undergo lengthier and more intensive training than was formerly the case; and

WHEREAS, podiatrists, having gained recognition relative to their functions in the prophylactic and minor surgical care of the foot are now demanding the right to membership on hospital staffs for the purpose of carrying out major surgical procedures on the foot and related areas; and

WHEREAS, there is no area of major foot surgery which cannot be better performed by orthopaedic specialists of the medical profession; now, therefore, be it

Resolved: That the CMA recommend that hospital staffs disapprove admission to hospital staff membership of practitioners of podiatry and strongly recommend to all members of the CMA that they refrain from participating as preceptors of podiatrists in major surgical procedures and that all members of the CMA should refrain from lending false respectability to the activities of podiatrists by participating in, and taking responsibility for, surgical procedures performed by podiatrists in hospital operating rooms; and be it further

Resolved: That the CMA request its representatives at the AMA level to request institutions of a similar policy on a national level.

ACTION: *Referred to Council for study before definitive action.*

Referred to: Commission on Hospital Affairs.

**BLUE SHIELD CONTRACT WITH MEDICARE
AND MEDI-CAL**

Resolution No. 45-68 Committee CPS

Introduced by: Peter Kunkel, M.D.

Representing: Alameda-Contra Costa Medical Association

Resolved: That this House recommend to the Board of Trustees of California Blue Shield that it consider the termination of its contract to administer a government program if demands made by such program upon California Blue Shield jeopardize the good working relationship between California Blue Shield and the physicians of this State.

ACTION: Above substitute resolution adopted.

Referred to: Blue Shield Board of Trustees.

1 1 1

**PRE-PAYMENT PROGRAM FOR
MEDI-CAL RECIPIENTS**

Resolution No. 46-68 Committee CPS

Introduced by: Peter Kunkel, M.D.

Representing: Alameda-Contra Costa Medical Association

WHEREAS, it is in the best interest of the medical profession as well as the public to seek out the most economical ways of delivering medical care of high quality to indigent citizens of this State; and

WHEREAS, it seems probable that the sharing of financial risk would act as a potent motive for economy; now, therefore, be it

Resolved: That this House encourage the acquisition by California Blue Shield of experience with prepayment programs for Medi-Cal recipients, incorporating the sharing of risks by the State, the fiscal intermediary and the providers of care.

ACTION: Adopted.

Referred to: CMA Executive Committee; Blue Shield Board of Trustees; Committee on Legislation; Officers of Component Medical Societies.

1 1 1

NATIONAL INFORMATION RETRIEVAL CENTER

Resolution No. 47-68 Committee 3A

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

WHEREAS, the problems of cancer, heart disease and stroke have been recognized as deserving urgent attention by both the medical profession and the people; and

WHEREAS, public funds have been made available to combat these diseases from all approaches; and

WHEREAS, the greatest weakness in the understanding and the treatment of these conditions is in the dissemination of accurate and up to date information to the profession; now, therefore, be it

Resolved: That this association urges the establishment of a national information retrieval center wherein should be stored all available information about these diseases. Appropriate regional information service centers linked to the national center and readily available to the profession should be established throughout the United States.

ACTION: Referred to CMA representatives to the California Committee on Regional Medical Programs.

Referred to: CMA representatives to California Committee on Regional Medical Programs.

1 1 1

PRESIDENT'S PAGE FOR CMA PRESIDENT

Resolution No. 48-68

Committee 3

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

ACTION: Withdrawn.

1 1 1

**EQUAL INDEMNITY FOR HOSPITAL
PRACTITIONERS AND PRIVATE PRACTITIONERS**

Resolution No. 49-68

Committee CPS

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

ACTION: No action was taken on this resolution.

1 1 1

VALUES UNDER MEDICARE

Resolution No. 50-68

Committee CPS

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

ACTION: Withdrawn by author.

1 1 1

**STUDY OF NON-UTILIZATION IN
CLOSED PANEL PLANS**

Resolution No. 51-68

Committee 3A

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

WHEREAS, lower rates of utilization of hospital, medical and surgical care in prepaid closed panel group plans are frequently cited as an indication of superior economies in the provision of medical care under such plans; and

WHEREAS, this lower rate of utilization has not been accurately measured; now, therefore, be it

Resolved: That the California Medical Association be asked to undertake a study to determine, insofar as feasible, the number of closed-panel subscribers who procure their medical care at their own expense from private practitioners in spite of the fact that they have already paid a premium for

this care to a closed panel plan which they do not choose to use.

ACTION: Referred to Council for further referral to the Bureau of Research and Planning.

Referred to: Bureau of Research and Planning.

1 1 1

PAYMENTS FOR PORTABLE X-RAY SERVICE IN NURSING HOMES

Resolution No. 52-68

Committee 3A

Introduced by: Stanley R. Truman, M.D.

Representing: Alameda-Contra Costa Medical Association

WHEREAS, under Section 1861.S3 of the Social Security Act as amended by Public Law 90-248 (H.R. 12080), an extended care facility is not defined as being a "patient's home," or residence, and

WHEREAS, any physician is prevented from billing his patient direct and receiving payment for portable x-rays performed under his supervision; now, therefore, be it

Resolved: That the California Medical Association recommend that with regard to the provision of such services, the extended care facility be defined as a residence in order that the physician may bill the patient for his professional services; and be it further

Resolved: That the Delegation to the American Medical Association request the Board of Trustees to secure, through its appropriate committee, a change in the Medicare regulations.

ACTION: Above substitute resolution adopted.

Referred to: AMA Delegation and Committee on Long-Term Care Facilities.

1 1 1

MOTORCYCLE LICENSING

Resolution No. 53-68

Committee 3B

Introduced by: Laurance A. Mosier, M.D.

Representing: Orange County Medical Association

WHEREAS, in the United States there are approximately one million new motorcycles registered annually; and

WHEREAS, deaths and injuries from motorcycles have doubled from 1962 to 1966 with a fatality rate per vehicle 11-18 times higher than for automobiles; and

WHEREAS, various studies have revealed that injuries and deaths of motorcycle riders are frequently due to inexperience and unfamiliarity with a motorcycle; and

WHEREAS, 20-30 percent of motorcycle deaths in studies occurred while riding rented or borrowed motorcycles; and

WHEREAS, a Californian with only a Learner's Permit can now rent a motorcycle; and

WHEREAS, New York, New Jersey, Maine, Oregon and Hawaii require special motorcycle licenses, issued after showing proficiency in handling a motorcycle; and

WHEREAS, this House of Delegates has previously supported efforts to obtain adequate licensing and safety requirements; and

WHEREAS, The Automotive and Traffic Safety Committee of the California Medical Association strongly endorses efforts to obtain adequate licensing requirements and desires reaffirmation by the House of Delegates; and

WHEREAS, it is desirable to have a valid operator's license for a four-wheeled vehicle prior to issuance of a motorcycle license; now, therefore, be it

Resolved: That the California Medical Association reaffirm its endorsement of efforts to secure legislation requiring special motorcycle licensing by the State Motor Vehicle Department; and be it further

Resolved: That the California Medical Association support Senate Bill 111 (Dills Bill) regarding motorcycle licensing and safety.

ACTION: Adopted.

Referred to: Committee on Legislation.

1 1 1

STANDARDS FOR ALCOHOL DETERMINATIONS IN BIOLOGICAL SPECIMENS

Resolution No. 54-68

Committee 3B

Introduced by: Laurance A. Mosier, M.D.

Representing: Orange County Medical Association

WHEREAS, scientific experiments have consistently demonstrated that tests for alcohol in biologic specimens are much more accurate than clinical examinations in identifying the presence of alcohol and the quantity ingested; and

WHEREAS, "Implied Consent" legislation has been passed by the California State Legislature in 1966 in recognition of this fact; and

WHEREAS, the Automotive and Traffic Safety Committee of the California Medical Association believes it is necessary for such tests to be sufficiently accurate to meet the needs of the courts, and to protect the public interest; now, therefore, be it

Resolved: That the California Medical Association approve and actively seek the establishment of statewide standards to insure that the collecting, analytical testing and reporting of alcoholic con-

centrations in biological specimens will be performed in a manner that meets scientific criteria for accuracy.

ACTION: *Adopted.*

Referred to: Committee on Automotive and Traffic Safety and Scientific Board.

1 1 1

PRESUMPTIVE LIMITS FOR BLOOD ALCOHOL

Resolution No. 55-68

Committee 3B

Introduced by: Laurance A. Mosier, M.D.

Representing: Orange County Medical Association

WHEREAS, alcohol is a positive factor in approximately 50 percent of traffic fatalities; and

WHEREAS, the National Safety Council Committee on Alcohol and Drugs has recommended that 100 mgm percent of blood alcohol be established as a presumptive limit of inebriation which represents a level consistently accompanied by objective evidence of deterioration of driving skills, even in chronic alcoholics; and

WHEREAS, the California Medical Association Automotive and Traffic Safety Committee strongly endorses 100 mgm percent of blood alcohol as a presumptive limit of "being under the influence of alcohol"; and

WHEREAS, the presumptive limit will not be construed as limiting the introduction of any other competent evidence bearing upon the question of whether the person was under the influence of alcohol, even though said alcohol may be less than 100 mgm percent; now, therefore, be it

Resolved: That the California Medical Association approve the presumptive limit of 100 mgm percent of blood alcohol and that efforts be made to support AB 147, establishing this level of blood alcohol as a presumptive limit of "being under the influence of alcohol."

ACTION: *Adopted.*

Referred to: Committee on Legislation.

1 1 1

PHYSICIANS' GUILD

Resolution No. 56-68

Committee 3

Introduced by: Marshall Stonestreet, M.D.

Representing: Orange County Medical Association

ACTION: *Not adopted.*

1 1 1

CHANGES IN PL 89-97 — RECERTIFICATION

Resolution No. 57-68

Committee 3A

Introduced by: Marshall Stonestreet, M.D.

Representing: Orange County Medical Association

WHEREAS, H.R. 12080 (Social Security Amendments of 1967) as passed makes steps in the right direction, but does not go far enough — in that it avoids certification, but not recertification; and

WHEREAS, the arguments against certification apply equally well against recertification; now, therefore, be it

Resolved: That the California Medical Association call on the Congress of the United States to eliminate recertification in the regulations pertaining to Public Law 89-97.

ACTION: *Adopted and referred to California delegation to the AMA.*

Referred to: AMA Delegation.

1 1 1

REPEAL OF ALL MEDICARE TYPE FEDERAL LEGISLATION

Resolution No. 58-68

Committee 3A

Introduced by: Marshall Stonestreet, M.D.

Representing: Orange County Medical Association

ACTION: *Not adopted.*

1 1 1

CHANGES IN PL 89-97 — DIRECT BILLING

Resolution No. 59-68

Committee 3A

Introduced by: Marshall Stonestreet, M.D.

Representing: Orange County Medical Association

WHEREAS, H.R. 12080 (Social Security Amendments of 1967) as passed makes steps in the right direction, but does not go far enough — in that it permits direct billing for some Title XIX patients, but not for others; and

WHEREAS, the arguments for direct billing apply equally well for all patients; now, therefore, be it

Resolved: That the California Medical Association call on the Congress of the United States to amend the laws and regulations pertaining to Public Law 89-97 to specifically permit direct billing on all Title XIX cases.

ACTION: *Adopted.*

Referred to: AMA Delegation.

1 1 1

PROTECTIVE HELMETS FOR MOTORCYCLISTS

Resolution No. 60-68

Committee 3B

Introduced by: Laurance A. Mosier, M.D.

Representing: Orange County Medical Association

WHEREAS, the motorcycle accident rate is twice the automobile accident rate, the death rate is 11-18 times higher; and

WHEREAS, approximately two-thirds of the deaths from motorcycles could be prevented by the

use of adequate protective helmets; and

WHEREAS, New York, Michigan, Georgia and several other states and all U.S. Military bases require the use of protective headgear when riding a motorcycle; and

WHEREAS, the cost of suitable helmets meeting the criteria of the American Standards Association (such as the Z-90.1-1966) is reasonable; and

WHEREAS, the California Medical Association has previously supported efforts to secure legislation requiring protective helmets for motorcyclists; and

WHEREAS, the California Medical Association Committee on Automotive and Traffic Safety desires reaffirmation of this endorsement; now, therefore, be it

Resolved: That the California Medical Association reaffirm its supportive efforts to secure legislation in California requiring the use by motorcyclists of protective helmets meeting the criteria of the American Standards Association and approved by the California Highway Patrol; and be it further

Resolved: That the California Medical Association support the passage of Senate Bill 111 (Dills Bill) and A.B. 289 (Forand and Deddeh) regarding the use of helmets by motorcyclists.

ACTION: Adopted.

Referred to: Committee on Legislation.

1 1 1

PL 89-749 AND 90-174 (COMPREHENSIVE HEALTH PLANNING)

Resolution No. 61-68

Committee 3A

Introduced by: Frank A. Rogers, M.D.

Representing: Los Angeles County Medical Association

ACTION: See Resolution No. 93-68 with which this resolution was combined.

1 1 1

TREATMENT OF OBESITY

Resolution No. 62-68

Committee 3B

Introduced by: William W. Waring, M.D.

Representing: Mendocino-Lake Medical Society

WHEREAS, increasing effort is being put into the search for new methods of regulating medical practice with the admirable intent of insuring the public a uniformly high quality of medical care; and

WHEREAS, there is a continuing need for medicine to demonstrate its competence in protecting the public against hazardous and unsound practice; and

WHEREAS, there is a significant and increasingly publicized problem with a certain minority of phy-

sicians who limit their practice to treatment of obesity; and

WHEREAS, digitalis, prolonged diuretic administration and toxic doses of thyroid, as well as other potentially dangerous therapeutic modalities, have no rational basis in the treatment of obesity alone; and

WHEREAS, office dispensing of drugs for obesity, which are readily available to patients through ethical pharmaceutical channels, is to be condemned; and

WHEREAS, in all instances where strong and potentially dangerous agents are administered, it is important to closely monitor the patient's response to these agents; now, therefore, be it

Resolved: That the Council of the CMA be directed to conduct an investigation of this type of practice for the purpose of safeguarding and informing the public; and be it further

Resolved: That the Council of the CMA, at its discretion, disseminate information through appropriate channels to the public, and be it further

Resolved: That the CMA Delegation introduce a similar request to the AMA House of Delegates.

ACTION: Above substitute resolution adopted.

Referred to: Scientific Board; AMA Delegation.

1 1 1

ANTICIPATION FOR FEDERAL PRESSURE FOR HEALTH LEGISLATION

Resolution No. 63-68

Committee 3A

Introduced by: Arthur Ablin, M.D.

Representing: Marin Medical Society

WHEREAS, the trend in federal legislation indicates that in the not-too-distant future extension of Medicare-like legislation to include people below 65 will occur; and

WHEREAS, anticipated and observed shortcomings of the Medicare Program have been experienced; and

WHEREAS, organized medicine can best influence such legislation if it anticipates the pressure which will occur for it and acts now to formulate a health program for people under 65 which will effectively and acceptably utilize the private sector; now, therefore, be it

Resolved: That

a. The CMA direct an appropriate committee to meet this challenge; and

b. It instruct its AMA Delegates to advise the AMA of the desirability of having a similarly directed committee.

ACTION: *Referred to Council for further referral to the Commission on Medical Services.*

Referred to: Commission on Medical Services.

1 1 1

MAINTENANCE OF PHYSICIAN COMPETENCE

Resolution No. 64-68

Committee 3

Introduced by: Marin Medical Society

WHEREAS, the periodic relicensing of physicians, based upon the certification of acceptable performance in continuing education programs or upon challenge examinations, has been recommended by the National Advisory Commission on Health Manpower as a means of maintaining the competence of physicians; now, therefore, be it

Resolved: That the Scientific Board of the CMA study the problem of maintaining the competence of physicians, study the possible solutions to the problem, including relicensure, and make appropriate recommendations to the Council.

ACTION: *Adopted.*

Referred to: Scientific Board.

1 1 1

NEW PHYSICIANS AND THE CMA

Resolution No. 65-68

Committee 3B

Introduced by: Marin Medical Society

WHEREAS, physicians just entering the private practice of medicine, though welcomed into our county, state and national medical societies, usually do not become active in society affairs for many years; and

WHEREAS, such new physicians in the community represent new thought, innovation and imagination; and

WHEREAS, their talents are being largely lost for years to our medical society; now, therefore, be it

Resolved: That the CMA investigate ways of drawing new member physicians into its organization to participate at all levels of deliberation and decision making.

ACTION: *Adopted.*

Referred to: Committee on Organizational Review and Planning.

1 1 1

ENCOURAGING HIGH SCHOOL STUDENTS IN MEDICINE AS A CAREER

Resolution No. 66-68

Committee 3B

Introduced by: Marin Medical Society

WHEREAS, the need for more physicians is continually increasing due to such factors as an expanding population, a broadening spectrum of treatable diseases, and an increasing demand for a

high level of medicine at all economic strata; now, therefore, be it

Resolved: That the CMA actively encourage and support component medical societies in forming organizations such as Future Doctor Clubs in order to interest top caliber high school students in the pursuit of medicine as a career.

ACTION: *Adopted.*

Referred to: Commission on Communications.

1 1 1

DANGEROUS DRUGS

Resolution No. 67-68

Committee 3

Introduced by: Joseph E. Turner, M.D.

Representing: Monterey County Delegation

WHEREAS, the possession and use of alcohol, a dangerous drug, is legal; and

WHEREAS, the possession and use of marijuana, a similarly dangerous drug, is a felony; and

WHEREAS, the possession and use of LSD, an admittedly more dangerous drug, is a misdemeanor; and

WHEREAS, the potential felony indictment for possession and use of marijuana has failed as a deterrent for thousands of adolescents; and

WHEREAS, focus upon the user of marijuana distracts our limited law enforcement agencies from solution of serious and significant crimes which are increasing in number; and

WHEREAS, the emphasis on the use of marijuana has created distrust and dissension in American homes of all socio-economic classes; now, therefore, be it

Resolved: That the CMA Council immediately establish a committee charged with the objective study of the pharmacology, physiology, and pathology of the drug marijuana, in order that the CMA may function as a responsible source of medical information to the state legislature; and be it further

Resolved: That the members of the committee prepare a written report for distribution to the House of Delegates at least thirty (30) days prior to the next annual meeting.

ACTION: *Referred to Scientific Board for further study.*

Referred to: Scientific Board.

1 1 1

MEDICAL ECONOMICS

Resolution No. 68-68

Committee 3A

Introduced by: Franklin Murphy, M.D.

Representing: Butte-Glenn Medical Society

WHEREAS, the economic problems associated

with the dissemination of health care services have become a social issue of foremost magnitude; and

WHEREAS, monumental changes in health care services are now being planned and accomplished without consultation and/or representation by organized medicine; and

WHEREAS, our commitment to mainstream medical care for everyone cannot be fulfilled unless new mechanisms for the medical care transaction are created; now, therefore, be it

Resolved: That

1. The CMA House of Delegates hereby declares that it considers the economic problems associated with the dissemination of health care services to be of paramount importance.

2. The Medical Services Commission and the Bureau of Research and Planning are instructed to study these problems in depth.

3. A report be submitted to the 1969 House of Delegates.

ACTION: Referred to Council for further referral to the Commission on Medical Services and the Bureau on Research and Planning.

Referred to: Commission on Medical Services; Bureau of Research and Planning.

1 1 1

NURSES TRAINING

Resolution No. 69-68

Committee 3B

Introduced by: Marshall Stonestreet, M.D.

Representing: Orange County Medical Society

Resolved: That the California Medical Association promote legislation that will require one year of internship to all Registered Nurses who are graduates with an A.A. degree (two year school) or with a B.A. degree (four year school), or the equivalent.

ACTION: Above resolution amended and referred to the Commission on Allied Health Professions and Services.

Referred to: Commission on Allied Health Professions.

1 1 1

MULTIPHASIC SCREENING PROGRAMS

Resolution No. 70-68

Committee 3B

Introduced by: Richard Wilbur, M.D.

ACTION: See Resolution No. 31-68 with which this resolution was combined.

Referred to: Commission on Community Health Services.

REIMBURSEMENT FOR INDIVIDUAL AND "LATE ENROLLEE" ATTENDING PHYSICIANS STATEMENTS

Resolution No. 71-68

Committee 3A

Introduced by: Richard Wilbur, M.D.

WHEREAS, most insurance companies have been reluctant to pay an appropriate fee for the preparation of "Attending Physicians Statements" for "late enrollees"; and

WHEREAS, the Chairman of the Northern California Medical Relations Committee of the Health Insurance Council has recently written, "we feel that such reimbursement is proper regardless of the company's reason for requesting the report"; now, therefore, be it

Resolved: That the California Medical Association recommends that all Attending Physicians Statements prepared for insurance companies be subject to the payment of an adequate fee regardless of the reason for the request and regardless of the fact that the individual may be a "late enrollee"; and be it further

Resolved: That the California Medical Association initiate correspondence with the various insurance companies involved and the Health Insurance Council requesting a change in the present policy since the cost for these services should be included in normal underwriting expenses.

ACTION: Adopted as amended and referred to Council for further referral to the Commission on Medical Services.

Referred to: Commission on Medical Services.

1 1 1

ECONOMICS

Resolution No. 72-68

Committee 3A

Introduced by: E. Kenneth Smith, M.D.

Representing: Humboldt-Del Norte County Medical Society

WHEREAS, medicine is continuously being criticized by public officials, legislators and the press for the rapid escalation of medical costs; and

WHEREAS, the many factors involved in this escalation, including deficit governmental spending with the resultant inflation, devaluation of the dollar and rising taxation, as well as the effects of scientific advances and advances in public demands on the time of physicians; now, therefore, be it

Resolved: That the Council of the California Medical Association institute an educational and informational program for federal and state officials, legislators, physicians, and appropriate groups of the general public, offering factual information, both historical and current, demonstrating

the effect of inflation, graduated income taxes, reduced productivity created by different time demands in current modes of practice and any other related items in the determination of fees by the individual practitioner.

ACTION: Referred to the Council.

Referred to: Division of Government Relations.

1 1 1

MEDICAL SERVICES REVIEW COMMITTEES

Resolution No. 73-68

Committee 3A

Introduced by: George C. Andersen, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, many members of our Association have labored long and diligently on medical services review committees in an attempt to help the State of California in its Medi-Cal Program, to assure, insofar as possible, mainstream care for the recipients of public welfare; now, therefore, be it

Resolved: That the CMA House of Delegates expresses its gratitude on behalf of the membership at large for the unselfish contribution of those of our members who have served on medical services review committees.

ACTION: Adopted.

1 1 1

PATIENT CARE AND RESPONSIBILITY

Resolution No. 74-68

Committee 3A

Introduced by: George C. Andersen, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, there has been and continues to be much concern regarding third party, especially governmental, intrusion into the traditional American physician-patient relationship and its attendant responsibilities; and

WHEREAS, there is continuing dialogue in an attempt to rationalize third party restrictions of quality and quantity of medical services while still providing mainstream medical care; now, therefore, be it

Resolved: That this House of Delegates reaffirms the inescapable responsibility of every physician, who undertakes a patient's care, to provide that patient with the best care within the capacity of the physician; and be it further

Resolved: That while each physician is free to choose his participation in any program, governmental or otherwise, that once he has accepted a given patient's care that it is his responsibility to make available the finest quantity and quality care within his capacity. He cannot abdicate this re-

sponsibility, dilute or restrict it, in the name or guise of third party restrictions or interference.

ACTION: Adopted.

1 1 1

PHYSICIAN PARTICIPATION IN THIRD PARTY MEDICINE

Resolution No. 75-68

Committee 3A

Introduced by: George C. Andersen, M.D.

Representing: Los Angeles County Medical Association

Resolved: That the California Medical Association reaffirms its support of the right, privilege and duty of each individual member to participate or not participate in any third party programs, including governmental, as the individual physician's conscience deems proper.

ACTION: Adopted.

1 1 1

CMA'S POSITION ON FREE CHOICE

Resolution No. 76-68

Committee 3A

Introduced by: George C. Andersen, M.D.

Representing: Los Angeles County Medical Association

ACTION: Not adopted.

1 1 1

DESIGNATION OF THE PHRASE (USUAL, CUSTOMARY, REASONABLE)

Resolution No. 77-68

Committee 3A

Introduced by: Frank R. Gondek, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, the CMA House of Delegates has adopted a resolution defining the meaning of the terms usual, customary, reasonable, in its Resolution No. 6, 1963; and

WHEREAS, by Resolution No. 21, 1964, the House of Delegates amended the definition of the term reasonable by changing "and" to "or," to read, a fee is "reasonable" when it meets the above two criteria (usual, customary), or in the opinion of the responsible Medical Association's Review Committee, is justifiable considering the special circumstances of the particular case in question; now, therefore, be it

Resolved: That the "Definition of Terms," Usual, Customary, Reasonable, approved by this House of Delegates in Resolution No. 21, 1964, hereafter be designated by the official phrase "Usual, Customary, or Reasonable."

ACTION: Adopted.

MILK PASTEURIZATION

Resolution No. 78-68 Committee 3
Introduced by: Lewis T. Bullock, M.D.
Representing: Los Angeles County Medical Association
ACTION: Withdrawn by author.

1 1 1

SOCIAL ECONOMIC RESEARCH

Resolution No. 79-68 Committee 3A
Introduced by: Homer C. Pheasant, M.D.
Representing: Los Angeles County Medical Association

WHEREAS, the Commission on Cost of Medical Care of the AMA did in June of 1964 present conclusions and recommendations to the Board of Trustees and expressed the hope "that the recommendations which are approved will help promote the wisest possible use of the medical care dollar and aid in the development of more meaningful data on the cost of medical care"; and

WHEREAS, the Commission further concluded that "there is a need for additional studies and qualified persons in the field of medical economics"; and

WHEREAS, Report F of the Board of Trustees, December 1964, though generally approving the Commission's recommendations did, however, modify and change it to conform to existing AMA facilities and staffing; and

WHEREAS, subsequent changes in the staffing and organizational structure of AMA did largely attenuate the effectiveness of these recommendations in that either these recommendations have been overlooked or neglected as to the intent of the House for a continuation and further studies in the field of social economics; and

WHEREAS, the cost of medical care continues to be a subject of major concern to all people in the United States; and

WHEREAS, in November of 1967 the AMA House of Delegates did recommend "that a committee of physicians approved by the Board of Trustees of the AMA or that a present existing council or commission of the AMA be instructed to study all methods of delivery of health care services presently in use; and *such new methods as may be proposed or developed*"; now, therefore, be it

Resolved: That this House of Delegates requests that the Board of Trustees of AMA review these prior activities of both themselves and this House, and take appropriate immediate action, either through the Department of Health Services of AMA, or through existing councils or committees; and be it further

Resolved: That the Board of Trustees of the AMA be requested to report to the House of Delegates of the American Medical Association at the June, 1968, Annual Session on action which they have taken pursuant to this resolution.

ACTION: Adopted.

Referred to: AMA Delegation.

1 1 1

MEDICAL EXAMINER

Resolution No. 80-68 Committee 3B
Introduced by: Lewis T. Bullock, M.D.
Representing: Los Angeles County Medical Association

WHEREAS, the law of the State of California requires every county to have a Coroner; and

WHEREAS, the Medical Examiner System is generally recognized as being a more efficient and reliable method of determining the cause of deaths which occur under medico-legal circumstances; now, therefore, be it

Resolved: That the Legislative Committee of the California Medical Association be requested to have legislation introduced which would allow any county so desiring to establish a Medical Examiner in place of a Coroner; and be it further

Resolved: That such Medical Examiner be required to be a pathologist; and be it further

Resolved: That the Legislative Committee report to the CMA Council of action taken before the 1969 House of Delegates Meeting.

ACTION: Adopted.

Referred to: Commission on Legislation.

1 1 1

PSYCHOLOGICALLY DISTURBED AND NEUROLOGICALLY HANDICAPPED CHILDREN

Resolution No. 81-68 Committee 3
Introduced by: Edward D'Orazio, M.D.
Representing: Los Angeles County Medical Association

WHEREAS, for the past year a special committee of the Southeast District of the Los Angeles County Medical Association has examined the various aspects of diagnosis, treatment and rehabilitation of psychologically disturbed and neurologically handicapped children in the Southeast District area specifically, and the greater Los Angeles area generally; and

WHEREAS, this study has confirmed that a significant number of children are so handicapped; and, that a large percentage of these youngsters can be assisted through qualified initiative and continuing medical diagnosis and treatment in concert with specialized educational programs when appropriate; and

WHEREAS, this study has determined that there is an increasing and continuing need to stimulate an awareness of and specialized knowledge about these problems among the medical profession; and to encourage cooperative coordinated efforts between the medical profession, educators and others; and

WHEREAS, this study has concluded that these problems may not be limited to Los Angeles County, but, in fact may exist throughout the State of California; now, therefore, be it

Resolved: That the California Medical Association and its component medical societies exert every effort in all appropriate areas to encourage the effective dissemination of information and the coordinated, cooperative and professional resolution of problems affecting the diagnosis, treatment and rehabilitation of psychologically disturbed and neurologically handicapped children.

ACTION: *Adopted as amended.*

Referred to: Committee on Mental Health.

CIGARETTE SMOKING

Resolution No. 82-68 Committee 3
Introduced by: Albert Fields, M.D.
Representing: Los Angeles County Medical Association

ACTION: *No action was taken on this resolution.*

PROFESSIONAL LIABILITY

Resolution No. 83-68 Committee 3B
Introduced by: Albert Fields, M.D.
Representing: Los Angeles County Medical Association

ACTION: *Not adopted.*

SENATE RESOLUTION 356

Resolution No. 84-68 Committee 3B
Introduced by: Albert Fields, M.D.
Representing: Los Angeles County Medical Association

Resolved: That California Senate Resolution 356 be commended by the CMA House of Delegates.

ACTION: *Above substitute resolution adopted.*

Referred to: Staff for implementation.

CHIROPRACTORS

Resolution No. 85-68 Committee 3A
Introduced by: Albert Fields, M.D.
Representing: Los Angeles County Medical Association

WHEREAS, the practice of chiropractic is an un-

scientific cult that impedes quality medical care; now, therefore, be it

Resolved: That this House support legislation prohibiting the payment of Medi-Cal, Medicare, Workmen's Compensation, Veterans Administration, and other funds to chiropractors and other unscientific cults.

ACTION: *Adopted and referred to the Council for further referral to the Committee on Legislation.*

Referred to: Committee on Legislation.

CPS REGULATION

Resolution No. 86-68 Committee CPS
Introduced by: Gordon T. Bowen, M.D.
Representing: Los Angeles County Medical Association

ACTION: *No action was taken on this resolution.*

PROPRIETARY HOSPITALS

Resolution No. 87-68 Committee 3B
Introduced by: Walter P. Ellerbeck, M.D.
Representing: Los Angeles County Medical Association

ACTION: *See Resolution No. 3-68 with which this resolution was combined.*

Referred to: Commission on Hospital Affairs.

PUBLIC LAW 89-749

Resolution No. 88-68 Committee 3A
Introduced by: Frank A. Rogers, M.D.
Representing: Los Angeles County Medical Association

ACTION: *See Resolution No. 93-68 with which this resolution was combined.*

NATIONAL ADVISORY COMMISSION ON HEALTH MANPOWER

Resolution No. 89-68 Committee 3B
Introduced by: Frank A. Rogers, M.D.
Representing: Los Angeles County Medical Association

ACTION: *No action was taken on this resolution.*

USUAL, CUSTOMARY OR REASONABLE FEE

Resolution No. 90-68 Committee 3A
Introduced by: Frank A. Rogers, M.D.
Representing: Los Angeles County Medical Association

Resolved: That the House of Delegates of the California Medical Association reaffirms its policy that the acceptable method of reimbursement by a third party should be on the basis of the usual, customary, or reasonable fee concept as previously defined by the House of Delegates.

ACTION: *Adopted.*

DEVELOPMENT OF STATISTICS
BY ORGANIZED MEDICINE

Resolution No. 91-68

Committee 3A

Introduced by: Frank A. Rogers, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, strong and growing pressures are being placed upon the medical profession to bring about its socialization; and

WHEREAS, many studies and data are being developed and widely promoted which would indicate that American medicine is in default or deficient or generally lacking in quality; and

WHEREAS, the majority of these studies are produced by federal bureaus or government sponsored agencies who believe in the state control of medicine; now, therefore, be it

Resolved: That the House of Delegates of the California Medical Association strongly reaffirms its belief that a free medical profession provides the best care at the most economical cost and urges the American Medical Association to use its resources in the immediate development of unbiased studies which will honestly confirm or countermand the statements of the Department of Health, Education and Welfare and other similar agencies.

ACTION: *Referred to Council for information.*

Referred to: Bureau of Research and Planning for information.

1 1 1

DEVELOPMENT OF COST STATISTICS FOR
PRIVATE VERSUS PUBLIC MEDICAL CARE

Resolution No. 92-68

Committee 3A

Introduced by: Frank A. Rogers, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, many studies and statements are being produced by government agencies and bureaus which purportedly show that the cost of private medical care is too high; and

WHEREAS, such studies inevitably indicate that the cost of private medical care, including doctors' fees, is too high; now, therefore, be it

Resolved: That the House of Delegates of the California Medical Association authorizes the Council of the Association to develop an independent fact finding study, which will report and make available to the membership and duly recognized organizations the true cost of private and public medical care; and be it further

Resolved: That such a study specifically contrast the cost of physicians' services on an in-patient and out-patient basis as well as the cost of proprietary

hospitals and government sponsored hospitals, such as those under the Veterans Administration.

ACTION: *Referred to Council for information.*

Referred to: Bureau of Research and Planning for information.

1 1 1

PUBLIC LAW 89-749

Resolution No. 93-68

Committee 3A

Introduced by: Frank A. Rogers, M.D., and Jean F. Crum, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, Public Law 89-749 (Comprehensive Health Planning) provides many opportunities for physician involvement and participation in the myriad activities related to personal and environmental health services; and

WHEREAS, the CMA Council adopted a policy statement of its ad hoc Task Force on P.L. 89-749 encouraging the leadership of component medical societies in the formation of areawide and regional voluntary comprehensive health planning councils; now, therefore, be it

Resolved: That the medical profession seek adequate representation on such councils and on their consultative committees; and be it further

Resolved: That the activities engaged in seeking to overcome existing deficiencies, wherever they are found, with respect to health services, manpower, and facilities; and be it further

Resolved: That the California Medical Association will attempt to work toward the improvement of P.L. 89-749 in order to make it a more effective instrument for comprehensive health planning; and be it further

Resolved: That the California Medical Association pursue corrective action through regulatory or legislative modification whenever regulations are promulgated which would interfere with sound medical practice.

ACTION: *Above substitute resolution adopted.*

Referred to: Task Force on Public Law 89-749 and AMA Delegation.

1 1 1

PHYSICIANS UNDER MEDICAL PROGRAM

Resolution No. 94-68

Committee 3A

Introduced by: Harry E. Hill, M.D.

Representing: Los Angeles County Medical Association

ACTION: *Because of its similarity with Resolution No. 28-68 no action was taken on this resolution.*

MAINSTREAM MEDICAL CARE

Resolution No. 95-68 Committee 3A

Introduced by: Charles D. Kranzdorf, M.D.

Representing: Los Angeles County Medical Association

ACTION: *No action was taken on this resolution because of its similarity with Resolution No. 42-68.*

1 1 1

BILLING PROCEDURES

Resolution No. 96-68 Committee 3A

Introduced by: R. Reed Austin, M.D.

Representing: Los Angeles County Medical Association

Resolved: That the members of the California Medical Association House of Delegates in regular session March 23 to 27, 1968, declare billing procedures under Title XIX unacceptable and urge both physicians and patients to work through their Congressmen to correct this inequitable situation by making billing procedures under Title XIX the same as those now under Title XVIII.

ACTION: *Adopted as amended.*

Referred to: AMA Delegation.

1 1 1

NEW BLUE SHIELD PROFESSIONAL PLAN

Resolution No. 97-68 Committee CPS

Introduced by: Wilbur G. Rogers, M.D.

Representing: Los Angeles County Medical Association

Resolved: That Blue Shield be commended for its efforts to develop a more satisfactory professional plan for physicians and their employees in response to the wishes of the House of Delegates; and be it further

Resolved: That the Blue Shield Board of Trustees be requested to conduct a continuing survey among California physicians to determine the various types of coverage desired in order to provide a base for future Blue Shield offerings of a health plan for physicians and their employees.

ACTION: *Above substitute resolution adopted.*

Referred to: Blue Shield Board of Trustees.

1 1 1

PAYMENT UNDER MEDICARE

Resolution No. 98-68 Committee 3A

Introduced by: Donald A. Adams, M.D.

Representing: Los Angeles County Medical Association

WHEREAS, it has apparently been the policy for Medicare insurance carriers to decline payment for certain *necessary* consultation; and

WHEREAS, insurance carriers have declined payment for certain *necessary* medical care of critically ill patients; and

WHEREAS, Medicare insurance carriers have declined payment to more than one doctor when such auxiliary medical care is *necessary*; now, therefore, be it

Resolved: That the CMA House of Delegates recommend to the AMA that Medicare, through its insurance carriers, be required to pay for *necessary* extended and auxiliary care, and consultation.

ACTION: *Referred to the Council.*

Referred to: Commission on Medical Services.

1 1 1

REVIEW PANELS IN MALPRACTICE INSURANCE

Resolution No. 99-68 Committee 3B

Introduced by: George Evashwick, M.D.

Representing: Los Angeles County Medical Association

ACTION: *No action was taken on this resolution.*

1 1 1

AFFIRMATION

Resolution No. 100-68 Committee 3

Introduced by: San Francisco Delegation

ACTION: *Withdrawn by author.*

1 1 1

WILBUR J. COHEN, ACTING SECRETARY OF HEW

Resolution No. 101-68 Committee 3A

Introduced by: Frank A. Rogers, M.D.; George C. Anderson, M.D.

Representing: Los Angeles County Medical Association

Be It Resolved: That the medical profession of California, through its House of Delegates here assembled, vigorously opposes the appointment of Wilbur J. Cohen to serve as the Secretary of Health, Education, and Welfare; and be it further

Resolved: That an all-out effort be made to have his appointment rejected by the Senate of the United States by:

1. Encouraging immediate communications from our membership and their friends to our U.S. Senators;

2. The sending of a formal telegram from the California Medical Association to the American Medical Association encouraging a similar campaign by all state societies;

3. The immediate communication of the first Resolve to each state medical society, the President of the United States, and the Senators from California; and

4. If time permits, instructing the Delegation from California to introduce a similar resolution

to the American Medical Association at its annual convention in June, 1968.

ACTION: Above substitute resolution adopted.

Referred to: Speaker and AMA Delegation.

1 1 1

REGULATIONS FOR SAFETY IN SCHOOL BUSES

Resolution No. 102-68

Committee 3B

Introduced by: Herman Stone, M.D.

Representing: Riverside County Medical Association

WHEREAS, 16 million (16,000,000) school children are transported daily by school buses over the city streets and rural highways of our nation; and

WHEREAS, fifty (50) children were killed and three thousand eight hundred (3,800) children were injured in school bus accidents in a recent year; and

WHEREAS, the UCLA Institute of Traffic and Transportation Engineering has recently completed exhaustive studies on "School Bus Passenger Protection to the Society of Automotive Engineers" (publication #670040); now, therefore, be it

Resolved: That the minimum standards for school buses in California should include:

1. Lap-type seat belts for all passengers. (The cross-chest lap-belt combination is not recommended for school bus passengers.)

2. Seat back height should be no less than 28 inches to provide adequate head support.

3. Seat anchorages should not fail from forward decelerations under 30 G.

4. Rigid structures should be padded with a minimum of ½ inch padding.

5. All vehicles classified as buses should include collision-resistant structure at both passenger car and truck bumper height.

6. Windows, preferably of a laminated glass with a high-energy interlayer, should stay in place and not pop out on impact.

7. Rigid protruding structures and force amplifying structures should be eliminated from the interior of the bus, where possible.

8. No standees should be permitted during transport of passengers.

9. School buses need at least four full-size emergency escape routes. Passengers should be acquainted with their location, and drilled in their emergency use.

ACTION: Referred to Council for further referral to the Committee on Automotive and Traffic Safety.

Referred to: Committee on Automotive and Traffic Safety.

CPS BYLAWS CHANGE

Resolution No. 103-68

Committee CPS

Introduced by: Frank A. Rogers, M.D.

Representing: Los Angeles County Medical Association

ACTION: Withdrawn by author.

1 1 1

PHYSICIAN UTILIZATION OF RURAL HOME HEALTH RESOURCES

Resolution No. 104-68

Committee 3

Introduced by: L. J. Snyder, M.D.

Representing: Fresno County

WHEREAS, organized medicine has long endorsed the concept of home health care and current health needs require the most economical use of health manpower and facilities in rural and urban areas consistent with quality care; and

WHEREAS, state and local medical societies are properly concerned with the availability and adequacy of rural health care services which support the work of the physician; now, therefore, be it

Resolved: That the California Medical Association formulate and help to implement, through the county medical societies, a program to encourage physicians to utilize rural home health services with local control as they deem advisable in their communities.

ACTION: Adopted.

Referred to: Commission on Community Health Services.

1 1 1

MARIJUANA

Resolution No. 105-68

Committee 3

Introduced by: Howard W. Lindsey, M.D.

Representing: San Mateo County Medical Society

WHEREAS, marijuana is known to be a dangerous drug; and

WHEREAS, the present laws making its possession a felony are sometimes inappropriate and hinder the efforts of the courts, the police and the community in effectively dealing with the problems of its usage; now, therefore, be it

Resolved: That the CMA (a) advise the legislators of the need for review of the laws relating to marijuana, (b) recommend that marijuana be considered as a dangerous drug inviting dependency rather than a narcotic drug, and (c) that the courts be given the discretion to consider the possession of marijuana as a felony or a misdemeanor, as they see fit for effective punishment.

ACTION: Above substitute resolution adopted as amended.

Referred to: Committee on Legislation.

LABORATORY MEDICINE

Resolution No. 106-68 Committee 3B
Introduced by: Osman H. Hull, M.D.
Representing: Monterey County Medical Society

WHEREAS, pathology, anatomical and clinical (Laboratory Medicine), developed in and is an integral part of medicine and its practice; and

WHEREAS, the growth in depth and breadth of medical knowledge has increased the utilization of and the dependence on laboratory medicine to maintain best patient care; and

WHEREAS, the technical component of laboratory medicine, test performance, may be properly and wisely delegated to specially trained and highly skilled paramedical personnel; and

WHEREAS, the performance of the professional components of laboratory medicine—selection, interpretation and application of the results of tests—demands a medical education and can be done only by physicians; now, therefore, be it

Resolved: That the California Medical Association reaffirm its time-honored stand that the practice of laboratory medicine is part of the practice of medicine, and that because of its increasing importance to patient care, involving mutual collaboration of physicians, the clinical laboratory must be directed actively by a physician.

ACTION: *Adopted as amended.*

1 1 1

CHANGE IN CALIFORNIA PHYSICIANS' SERVICE BYLAWS

Resolution No. 107-68 Committee CPS
Introduced by: Richard S. Wilbur, M.D.
Representing: California Blue Shield

Resolved: That Chapter X, Section 1, of the Bylaws of California Physicians' Service be amended to read as follows:

"Chapter X—Funds; Section 1—Investment of Funds—

"Funds of this corporation not required for current operating expenses may be invested prudently in public or corporate securities, with reasonable diversification; provided that, not more than twenty-five percent of invested funds may be represented by unsecured corporate shares."

ACTION: *Adopted.*

Referred to: Blue Shield Board of Trustees.

1 1 1

BUSINESS & PROFESSIONS CODE

Resolution No. 108-68 Committee 3B
Introduced by: San Francisco Delegation

ACTION: *See Resolution No. 19-68 with which this resolution was combined.*

THERAPEUTIC ABORTION

Resolution No. 109-68 Committee 3
Introduced by: San Francisco Delegation

Resolved: That the California Medical Association encourage legislation which will allow therapeutic abortion to be done when there is substantial risk of grave physical or mental defect in the product of conception.

ACTION: *Adopted as amended.*

Referred to: Committee on Legislation.

1 1 1

FINANCIAL SUPPORT, THE CALIFORNIA TUMOR TISSUE REGISTRY

Resolution No. 110-68 Committee 2
Introduced by: Jean F. Crum, M.D.

ACTION: *Withdrawn by author.*

1 1 1

MALCOLM C. TODD, M.D.

Resolution No. 111-68 Committee 3
Introduced by: The Council

WHEREAS, the American Medical Association House of Delegates approved the establishment of the American Medical Political Action Committee in 1961 as an independent, voluntary, non-profit and bipartisan organization to promote political education and political action; and

WHEREAS, the California delegation to the 1962 clinical session of the AMA provided the initial stimulus for an annual national AMPAC membership campaign; and

WHEREAS, Doctor Malcolm C. Todd has served as a distinguished member of the AMPAC National Board of Directors for six years and is still active on that board; and

WHEREAS, Doctor Todd also served as President of the Public Health League of California and later became the first chairman of the independent California Medical Political Action Committee (CALPAC); and

WHEREAS, Doctor Todd has dedicated himself for many years to alerting physicians and their wives to the vital necessity for becoming effectively involved in political education and political action; now, therefore, be it

Resolved: That this House of Delegates warmly commends Doctor Todd for his invaluable contributions to medicine's now fully respected position as a sophisticated participant in political activities; and be it further

Resolved: That the members of this House of Delegates urge the leaders of local medical organizations to renew their endorsement of CALPAC

and AMPAC and accelerate their efforts to assure the continued growth and effectiveness of these vital organizations.

ACTION: Adopted.

Referred to: Division of Government Relations.

1 1 1

ALCOHOLISM

Resolution No. 112-68

Committee 3B

Introduced by: Lewis T. Bullock, M.D.

Resolved: That the California Medical Association strongly urges that each local medical society appoint a Committee on Alcoholism.

ACTION: Adopted.

Referred to: Medical Executives Conference and Component Society Presidents.

1 1 1

CARRIER CONCEPT AND PHYSICIAN REIMBURSEMENT UNDER MEDI-CAL

Resolution No. 113-68

Committee 3A

Introduced by: Albert G. Miller, M.D.

Representing: The Council

WHEREAS, Medi-Cal legislation as enacted into law stipulates that the State shall, to the extent feasible, contract with carriers to provide or arrange services through health benefit plans; and

WHEREAS, the law further provides that in determining the reasonable charge for a physician's services, there shall be taken into consideration the customary charge for similar services generally made by the physician, as well as the prevailing charges in the locality for similar services thereby making available to indigent and medically indigent people mainstream medical care; and

WHEREAS, the California Medical Association strongly supported these principles in urging the enactment of this law; and

WHEREAS, these principles allow and make it possible for the State to benefit from extensive carrier medical administrative experience and also to gain the necessary cooperation of the medical profession with its system of "peer review committees" which assist the carrier in properly assessing and adjudicating charges for physicians' services; and

WHEREAS, the Federal law clearly establishes the role of the carrier as a buffer between government and vendors of health care services, as well as establishing the concept of vendor reimbursement for services on the basis of customary and prevailing charges; and

WHEREAS, these accepted standards would be eliminated by the enactment of certain current proposals; and

WHEREAS, such proposals would negate the in-

tent of the Medi-Cal program, eliminate mainstream care, seriously impair the administration of the program, and directly jeopardize physician cooperation in the program; now, therefore, be it

Resolved: That the House of Delegates of the California Medical Association reaffirms its previous position on the principle of free choice of physician and facility, the necessity of maintaining the role of the carrier, the principle of physician reimbursement for services based on usual and customary charges; and be it further

Resolved: That the California Medical Association cannot advise its membership, the legislature or the general public to support any program unless these essential elements are retained; and be it further

Resolved: That copies of this resolution be forwarded to the Governor of the State of California, the President of the State Senate, the Speaker of the State Assembly, the Chairman of any State Legislative Committees involved in Medi-Cal hearings or studies, and to all Directors of State agencies involved in the administration of the Medi-Cal program.

ACTION: Adopted.

Referred to: Division of Government Relations for transmittal.

1 1 1

PREPAYMENT CONCEPT FOR MEDI-CAL

Resolution No. 114-68

Committee CPS

Introduced by: Albert G. Miller, M.D.

Representing: The Council

Resolved: It is the judgment of CMA that the most satisfactory mechanism to pay for physician services for Medi-Cal beneficiaries would be for the State to contract with a carrier under which the State would pay a premium per month, per eligible recipient, and the carrier would pay for physicians' services on a true shared risk basis; and be it further

Resolved: That CMA House of Delegates request Blue Shield to develop such a program to cover payment for physicians' services under Medi-Cal.

Resolved: That the San Joaquin Valley Medical Society and its Foundation for Medical Care be commended for establishing in conjunction with California Blue Shield the first such prepayment bill on record in the United States as of 1 February 1968 in the hope of obtaining statistics and experience which can benefit California medicine in this field.

ACTION: Adopted as amended.

Referred to: CMA Executive Committee; Blue Shield Board of Trustees; Committee on Legislation; Officers of Component Medical Societies.

AMENDMENTS TO CONSTITUTION AND BYLAWS

Amendments to the Constitution and Bylaws may be introduced at any session of the House of Delegates. Amendments to the Bylaws may be acted upon 24 hours after introduction, while amendments to the Constitution must lie on the table until the next regular meeting of the House of Delegates.

Reference Committee No. 4 considers all proposed amendments to both the Constitution and the Bylaws. Under the required waiting periods, all Constitutional amendments introduced in 1967 were brought before the House of Delegates for action in 1968.

ACTIONS

Listed below are actions taken by the House of Delegates on all proposed amendments to the Constitution and Bylaws presented for action this year. A two-thirds affirmative vote is required for passage of all amendments. New language is shown in italics.

1967

CONSTITUTIONAL AMENDMENT ACTED UPON IN 1968

One Constitutional amendment was introduced in the 1967 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed Constitutional amendment was printed in two issues of CALIFORNIA MEDICINE before it came before the House of Delegates for action.

1 1 1

CONSTITUTIONAL AMENDMENT NO. 1-67

Woman's Auxiliary; Article I, Sec. 6

Introduced by: The Council

Resolved: That a new Section 6 be added to Article I, as follows:

"Section 6.—Woman's Auxiliary to the California Medical Association.

"In addition to the organizational structure previously set forth in this Article, this Association may charter a Woman's Auxiliary to the California Medical Association, and components thereto, which shall be considered an integral part of the Association but which shall conduct its own organ-

ization and business separate and distinct from the Association and its Societies, subject to the following requirements:

"a. The name of the Auxiliary shall be 'Woman's Auxiliary to the California Medical Association,' (hereinafter referred to as Auxiliary);

"b. The purpose of the Auxiliary shall be to promote the science and art of medicine, the protection of public health and the betterment of the medical profession, and to promote similar interests of its component Auxiliaries;

"c. The Auxiliary shall be composed of the component Auxiliaries and their members;

"d. Component Auxiliaries shall include all women's auxiliaries to component Medical Societies of the California Medical Association heretofore or hereafter chartered by this Association;

"e. Charters to component Auxiliaries shall be granted and revoked by the Association as it may provide; provided that no charter issued by the Association, nor any action of the Association in issuing or revoking such charters, shall conflict with the purposes and principles of this Association as set forth in its Constitution and Bylaws."

ACTION: *Adopted.*

1968 BYLAW AMENDMENTS

ORDERLY PROCEDURE FOR DISTRICT WITHDRAWAL, CHAPTER I, SECTION 4

Bylaws Amendment 13-68

Committee 4

Introduced by: Jay J. Crane, M.D.

Representing: House of Delegates ad hoc Committee

Resolved: That Section 4 is hereby added to Chapter I of the Bylaws of this Association, California Medical Association, to read as follows:

Section 4.—Component District Withdrawal.

In the event that any qualified component district of a component medical society desires to be separately chartered by this Association, as authorized in Article I of the Constitution, it, the component society affected and this Association shall proceed as follows:

1. A petition signed by at least 10 percent of the active members of a component District of 300 or more members, established by a component society, for an election to determine whether or not such established District should exercise its option to withdraw from the component society, shall be

presented to the governing body of the component society, and the governing body, after checking the petition to determine if there were a qualified number of signatures thereon, shall immediately notify the Officers and governing body of the District Society, and the Council of this Association, that such a petition has been received, checked and qualified; and request this Association to conduct a mail ballot of the district on the proposition of whether or not the established component District should exercise its option to withdraw from the component society.

2. The component society, upon receipt of such notification, shall immediately certify to the CMA and to the established District from which the petition came, a list of the active members within said District entitled to vote upon the question. The component society shall have not more than 30 days from the date of the receipt of the petition to certify such list of members.

3. This Association, upon receipt of said petition, and the certified list of voters from the component society, shall, within a specified time as outlined hereinafter, cause to be mailed to all voters within the established District, the question "Shall District of Medical Society exercise its option to withdraw from Component Medical Society, and set up and establish a new and separate component medical society of this Association, to be hereafter known as Medical Society?" The Council of this Association shall fix the time for said election to be held not less than sixty (60) days nor more than one hundred twenty (120) days following the receipt of the petition.

4. There shall be included within the envelope containing the mail ballot, such statements as have been submitted to the CMA, both pro and con. Such statements shall only contain pertinent arguments and facts, for and against said withdrawal, and shall be accepted by an Election Committee appointed by the Council of this Association, consisting of members of the Association who are not members of the established District or the component society involved in the withdrawal procedure.

5. A two-thirds affirmative vote of the active members voting, provided a majority of the active members vote, shall be necessary to exercise the option of withdrawal.

6. Ballots shall be sent out thirty (30) days prior to the ballot counting.

7. If the necessary affirmative vote of the active members of the District is obtained, the secretary of this Association shall so report to the next session of the House of Delegates and shall request

the House to authorize the issuance of a charter to such District.

8. A charter issued pursuant to this Section 4 shall become effective on the next ensuing 1 December, provided that prior thereto the charter recipient may organize, adopt a Constitution and Bylaws, elect officers and must, prior to 31 August, notify this Association of its roster of members. It is further provided that dues paid in the calendar year of charter issuance shall belong to the organization to which payment was made by or on behalf of each member, and the newly chartered society may establish and collect dues for each calendar year commencing after the 1 December effective date.

9. A component District that becomes a chartered component society of this Association, pursuant to this Section, shall be included within District Number Twelve of the Councilor Districts as set forth in Section 10, Part B, Article III, of the Constitution of this Association.

ACTION: Adopted as amended.

1 1 1

RETIRED MEMBERSHIP, CHAPTER II, SECTION 4

Bylaws Amendment 2-68

Committee 4

Introduced by: Henry J. Rulfo, M.D.

Representing: Ventura County Medical Society

Resolved: That Chapter II, Section 4(a) of the Bylaws of the California Medical Association be amended by inserting the language in italics, so that the section shall read:

(a) Retired Members. The Council, on recommendation of any component society, may grant retired membership to those active and associate members who have ceased the practice of medicine to the extent and for reasons satisfactory to such component society and the Council, who have been active members of the Association for a total of ten years prior thereto, *or who have continuously been active members of the California Osteopathic Association, the Forty First Medical Society and any component society for a total of ten years prior thereto*, and who have paid dues for the current or immediately preceding year, and those retired physicians who have moved to California and who have been active members of another State association or the American Medical Association for a total of ten years prior thereto. Retired membership shall endure as long as the retired member does not engage in full time practice of medicine; but in the event that a member classified as retired resumes active, full time practice of medicine such resumption shall automatically terminate retired membership and reestablish active membership.

Upon resumption of full time practice by any retired member, the secretary of his component society shall transfer such member from the retired classification to the active classification and notify the secretary of this Association, who shall do likewise with respect to the membership rolls of this Association.

ACTION: Adopted.

1 1 1

COMMITTEE ON ACCREDITATIONS, CHAPTER IV, SECTION 2

Bylaws Amendment 3-68

Committee 4

Introduced by: The Council

Resolved: That Chapter IV, Section 2 be amended by adding subsection (j), which reads as follows: (New language in italics.)

(j) *Committee on Accreditations. This Committee shall be responsible for implementing the program of the Scientific Board on voluntary accreditation of postgraduate courses.*

ACTION: Adopted.

1 1 1

EXECUTIVE COMMITTEE, CHAPTER VI, SECTION 6

Bylaws Amendment 4-68

Committee 4

Introduced by: The Council

Resolved: That Chapter VI, Section 6, of the bylaws of this Association, California Medical Association, is hereby amended by deleting the present Section 6, language in parentheses, and inserting in lieu thereof a new Section 6, as follows: (New language is in italics.)

(Section 6.—Advisory Committee for Emergency Action)

(The Advisory Committee for Emergency Action shall consist of the president, the president-elect, the chairman of the Council and the speaker of the House of Delegates.)

(It shall have no policy making powers and shall function only under the direction of the Council. Its actions shall be subject to review and approval by the Council and it shall act only on matters requiring urgent decision while the Council is not in session.)

Section 6.—Executive Committee of the Council

The Executive Committee of the Council shall consist of the president, as chairman, the president-elect, chairman of the Council, Speaker of the House of Delegates and the immediate past president.

This committee has the power and authority to transact Association business of an emergency or

unusual nature between Council meetings, in consonance with stated Council policy.

All transactions of this committee shall be reported in full at the next regularly scheduled meeting of the Council, and shall be subject to Council review and appropriate action.

ACTION: Adopted as amended.

1 1 1

COMMISSION ON PUBLIC AGENCIES, CHAPTER VII, SECTION 1

Bylaws Amendment 5-68

Committee 4

Introduced by: The Council

Resolved: That Chapter VII, Section 1, Subsection (b) of the Bylaws of this Association be amended by deleting the words in parentheses and adding the words in italics, so that it reads as follows:

(b) Commission on Public Agencies, responsible for the activities of and through which the following standing committees shall report:

1. Committee on Public Health,
2. Committee on Mental Health,
3. Committee on Welfare Medical Care Programs,
4. Committee on (Occupational Health and) *Physical Medicine and Rehabilitation.*

ACTION: Adopted.

1 1 1

COMMISSION ON COMMUNITY HEALTH SERVICES, CHAPTER VII, SECTION 1

Bylaws Amendment 6-68

Committee 4

Introduced by: The Council

Resolved: That Chapter VII, Section 1, Subsection (c) of the Bylaws of this Association be amended by deleting the period after Committee on Blood Banking and inserting a comma, and by adding the words in italics, so that Subsection (c) will read as follows:

(c) Commission on Community Health Services, responsible for the activities of and through which the following standing committees shall report:

1. Committee on Rural Health,
2. Committee on School Health,
3. Committee on Health Care for the Aging,
4. Committee on Disaster Medical Care,
5. Committee on Automotive and Traffic Safety,
6. Committee on Medical Aspects of Sports and Physical Fitness,

7. Committee on Environmental Health,
8. Committee on Blood Banking,
9. *Committee on Alcoholism,*
10. *Committee on Emergency Medical Care,*
11. *Committee on Occupational Health.*

ACTION: *Adopted.*

1 1 1

**COMMISSION ON ALLIED
HEALTH PROFESSIONS AND SERVICES,
CHAPTER VII, SECTION 1**

Bylaws Amendment 7-68

Committee 4

Introduced by: The Council

Resolved: That Chapter VII, Section 1, Subsection (g) of the Bylaws of this Association be amended by deleting the language in parentheses and adding the words in italics, so that this subsection shall read:

(g) Commission on Allied Health Professions and Services, responsible for the activities of and through which the following standing committees shall report:

1. Committee on (Paramedical) *Allied Health Personnel,*
2. Committee on Other Professions,
3. Liaison Committee to the California Medical Assistants Association,
4. Committee on Medicine and Religion,
5. Committee on Voluntary Health Agencies.

ACTION: *Adopted.*

1 1 1

**COMMISSION ON HOSPITAL AFFAIRS,
CHAPTER VII, SECTION 1**

Bylaws Amendment 8-68

Committee 4

Introduced by: The Council

Resolved: That Chapter VII, Section 1, Subsection (h) of the Bylaws of this Association be amended by deleting the period after Committee on Health Facilities Planning and inserting a comma, and by adding the words in italics, so that Subsection (h) shall read as follows:

(h) Commission on Hospital Affairs, responsible for the activities of and through which the following standing committees shall report:

1. Medical Staff Survey Committee,
2. Committee on Health Facilities Planning,
3. *Committee on Long-Term Care Facilities.*

ACTION: *Adopted.*

**ELECTION OF OFFICERS: TERMS,
CHAPTER VIII, SECTION 1**

Bylaws Amendment 1-68

Committee 4

Introduced by: Leon P. Fox, M.D.

Representing: Santa Clara County Medical Society

ACTION: *Not adopted.*

1 1 1

**DUTIES OF THE PRESIDENT,
CHAPTER IX, SECTION 1**

Bylaws Amendment 9-68

Committee 4

Introduced by: The Council

Resolved: That Chapter IX, Section 1, of the Bylaws of this Association be amended by deleting the language in parentheses and adding the words in italics, so that the new section will read:

Section 1.—Duties of the President

(The President shall preside at all meetings of the Association.)

He shall be the (real head) *leader and official spokesman* of the profession of the state during his term of office, (and). *As far as practicable* he shall visit, by appointment, the various sections of the state and assist the councilors in building up the component societies, and in making their work more practical and useful. The Council shall decide what portion of the expenses incurred on his official visits shall be paid by the Association.

He shall appoint all committees not otherwise provided for; he shall deliver an address at the regular session at such time as may be arranged, and shall perform such other duties as custom and parliamentary usage may require, or as the House of Delegates or the Council may direct.

He shall be ex officio a member of all committees of the Association.

ACTION: *Adopted as amended.*

1 1 1

**DUTIES OF THE EXECUTIVE DIRECTOR,
CHAPTER IX, SECTION 2**

Bylaws Amendment 10-68

Committee 4

Introduced by: The Council

Resolved: That Chapter IX, Section 2 of the Bylaws of this Association be amended by deleting the language in parentheses and adding the words in italics, so that the new section will read:

Section 2.—Duties of the Executive Director (and Field Representatives)

The duties of the Executive Director (and Field Representatives) may be such as are delegated to (them) *him* by the Council, and may be any and

all duties as are specified under the various provisions of this section.

((a) Minutes. The secretary shall attend the general meetings of the Association, the meetings of the House of Delegates and of the Council and shall keep minutes of their respective proceedings in separate record books.)

((b)) (a) Custodian of Records. He shall be custodian of all record books and papers belonging to the Association. He shall have the custody of the seal of the Association.

((c)) (b) Contracts. He shall countersign all contracts, agreements, conveyances, transfers or other instruments to which the Association is a party, the execution of which has been authorized by the House of Delegates or Council.

((d)) (c) Checks. The (secretary) *director* shall sign and issue checks or drafts only upon vouchers approved and signed by at least two of the members of the Finance Committee or as otherwise provided.

((e) Advertisements in Association Publications. The secretary, subject to instructions by the Council, shall carefully examine, approve, modify or reject all material for advertising in any of the publications of the Association, and shall, in all cases of doubt, refer such proposed advertisements to the Council for decision. He shall, with the approval of the Council, execute, for the Association, written contracts relating to advertising in the form approved by the Council, subject to instructions by the Council.)

((f)) (d) Registrar at Annual Sessions. He shall provide for the registration of the members and delegates at the Annual Session.

((g)) (e) Index Register of California Medical Licentiates. He shall, with the cooperation of the secretaries of the component societies, keep a (card index register of all the licensed practitioners of the state by counties,) *current record of all members of the Association by component societies*, noting the status of each in relation to his component society; and shall transmit a copy of this list to the American Medical Association, transmitting to its secretary each month a report containing the names of new members and the names of those dropped from the membership roster during the preceding month.

Subparagraphs (h), (i), (j), (k), (l), (m), (n), (o), (p), (q) and (r) shall remain the same, except that they would be re-lettered (f), (g), (h), (i), (j), (k), (l), (m), (n), (o) and (p).

ACTION: *Adopted.*

DUTIES OF THE SECRETARY, CHAPTER IX, SECTION 8

Bylaws Amendment 11-68

Committee 4

Introduced by: The Council

Resolved: That Chapter IX be amended by adding a new Section 8, to read as follows:

Section 8.—Duties of the Secretary

The duties of the secretary shall be such as are delegated to him by the Council and, specifically, shall be as follows:

(a) *Minutes. The secretary shall attend the general meetings of the Association, the meetings of the House of Delegates and of the Council and shall keep minutes of their respective proceedings in separate record books.*

(b) *Advertisements in Association Publications. The secretary, subject to instructions by the Council, shall carefully examine, approve, modify or reject all material for advertising in any of the publications of the Association, and shall, in all cases of doubt, refer such proposed advertisements to the Council for decision. He shall, with the approval of the Council, execute, for the Association, written contracts relating to advertising in the form approved by the Council, subject to instructions by the Council.*

ACTION: *Adopted.*

‘ ‘ ‘

PREPARATION OF BUDGET, CHAPTER X, SECTION 1

Bylaws Amendment 12-68

Committee 4

Introduced by: The Council

Resolved: That Chapter X, Section 1, of the Bylaws of this Association be amended by adding the words “for appropriate action” at the end of the section, so that the last paragraph shall read: (New words in italics.)

Prior to the Annual Session in each year the Finance Committee shall present the proposed budget to the Council for its approval, and the budget as approved by the Council shall be submitted by it to the House of Delegates *for appropriate action.*

ACTION: *Adopted.*

‘ ‘ ‘

FOR ACTION IN 1969

One Constitutional amendment was introduced in the 1968 House of Delegates and, under the terms of the Constitution, must lie on the table

until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. In addition, the proposed Constitutional amendment is required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

1 1 1

CHARTERS, ARTICLE I, SECTION 5

Constitutional Amendment 1-68

Committee 4

Introduced by: The Council

Resolved: That Article I, Section 5 of the Con-

stitution of this Association be amended by deleting the language in parentheses, so that the section will now read:

Section 5.—Component Society Charters

Charters to component societies may be granted and revoked as hereinafter prescribed. (, subject to the limitation that only one charter may be outstanding at any one time in any county.)

(Notwithstanding the foregoing,) One charter may be issued to a component society that is not limited as to geographical area or which overlaps the area covered by one or more existing component societies.

❧ In Memoriam ❧

AMYES, LOWELL SYDNEY, Van Nuys. Died 12 May 1968 in Northridge of coronary thrombosis, aged 45. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1946. Doctor Amyes was a member of the Los Angeles County Medical Association.



ANDERSON, RICHARD L., Eureka. Died 27 May 1968 in Eureka of cancer, aged 44. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1948. Licensed in California in 1948. Doctor Anderson was a member of the Humboldt-Del Norte County Medical Society.



BIRKENFELD, LEE WEINGARTEN, Castro Valley. Died 23 May 1968, aged 44. Graduate of New York University College of Medicine, New York, 1951. Licensed in California in 1955. Doctor Birkenfeld was a member of the Alameda-Contra Costa Medical Association.



BOLANDER, WILLIAM D., Loma Linda. Died 10 May 1968 in Baldwin Park, aged 35. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1958. Licensed in California in 1960. Doctor Bolander was a member of the San Bernardino County Medical Society.



BRINER, CONRAD CHARLES, Auburn. Died 27 April 1968 in Auburn, aged 72. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1925. Licensed in California in 1925. Doctor Briner was a retired member of the Placer-Nevada County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



BUCKINGHAM, JOHN ROYAL, Los Angeles. Died 3 May 1968 in Los Angeles of coronary thrombosis, aged 80. Graduate of California Eclectic Medical College, Los Angeles, 1915. Licensed in California in 1915. Doctor Buckingham was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



BUCKLEY, ELIZABETH J., Santa Rosa. Died 30 March 1968, in Santa Rosa of cancer, aged 40. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1957. Licensed in California in 1959. Doctor Buckley was a member of the Sonoma County Medical Society.

COMPTON, CLARENCE SUMNER, Bakersfield. Died 23 December 1967, aged 85. Graduate of Los Angeles Medical Department, University of California, 1912. Licensed in California in 1912. Doctor Compton was a member of the Kern County Medical Society.



GARDNER, DON G., San Francisco. Died 23 May 1968 in San Francisco of cancer, aged 57. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1939. Licensed in California in 1939. Doctor Gardner was a member of the San Francisco Medical Society.



GARDNER, DONALD L., Glendale. Died 18 May 1968 in Glendale of myocardial infarction, aged 58. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Doctor Gardner was a member of the Los Angeles County Medical Association.



KAHN, BERNARD I., San Francisco. Died 31 May 1968 in San Francisco of acute coronary occlusion, aged 59. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1934. Licensed in California in 1953. Doctor Kahn was a member of the San Francisco Medical Society.



MCGETTIGAN, DANIEL LOUIS, San Francisco. Died 12 May 1968 in San Francisco of heart disease, aged 53. Graduate of St. Louis University School of Medicine, Missouri, 1940. Licensed in California in 1940. Doctor McGettigan was a member of the San Francisco Medical Society.



MOELLER, HUGO CHARLES, San Francisco. Died 1 June 1968 in San Francisco, aged 44. Graduate of The University of Chicago, The School of Medicine, Illinois, 1948. Licensed in California in 1956. Doctor Moeller was a member of the San Francisco Medical Society.



MORTENSEN, JOHN P., Loma Linda. Died 28 February 1968 in Loma Linda of Hodgkin's disease, aged 77. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1921. Licensed in California in 1921. Doctor Mortensen was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

NEIL, JAMES M., Oakland. Died 15 April 1968 in Oakland of myocardial failure due to chronic pulmonary emphysema, aged 69. Graduate of Medical College of South Carolina, Charleston, 1923. Licensed in California in 1924. Doctor Neil was a member of the Alameda-Contra Costa Medical Association.



OJA, RAYMOND O., San Francisco. Died 22 May 1968 in Tracy from injuries suffered in an automobile collision, aged 39. Graduate of State University of New York College of Medicine at Syracuse, New York, 1952. Licensed in California in 1954. Doctor Oja was a member of the San Francisco Medical Society.



OLSEN, JACK GORDON, Santa Monica. Died 14 May 1968 in Los Angeles, aged 43. Graduate of the University of Minnesota Medical School, Minneapolis, 1948. Licensed in California in 1955. Doctor Olsen was a member of the Los Angeles County Medical Association.



SANDS, RAYMOND, A., Santa Monica. Died 14 May 1968 in Santa Monica of coronary thrombosis, aged 79. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1913. Licensed in California in 1913. Doctor Sands was a member of the Los Angeles County Medical Association.

SCHOFIELD, RICHARD OSLER, Sacramento. Died 16 May 1968 in Sacramento, aged 79. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1922. Licensed in California in 1923. Doctor Schofield was a retired member of the Sacramento County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



STEVENSON, SAMUEL LOWELL, Walnut Creek. Died 18 May 1968 in Walnut Creek, aged 72. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Stevenson was a member of the San Francisco Medical Society.



TETZLAFF, FRED MARTIN, San Francisco. Died 19 May 1968, aged 48. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1945. Doctor Tetzlaff was a member of the San Francisco Medical Society.



WIENHOLZ, PETER PAUL, San Francisco. Died 18 May 1968 in San Francisco, aged 81. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1920. Licensed in California in 1920. Doctor Weinholz was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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OF THE CALIFORNIA MEDICAL ASSOCIATION

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PUBLIC HEALTH REPORT

Hamlet C. Pulley, M.D., M.P.H.

Acting Director*, State Department of Public Health

Comprehensive Health Planning in California

THE EXPRESSION "comprehensive health planning," should be looked at critically and its meaning carefully considered. The universe encompassed is really the size of the interface between the healing arts and the populace around them—the environment in which the health services are provided, the ills of the people and the way they express those ills, and the way the healing arts respond to the needs of the people. This means that planning must focus on that interface, but broaden its field of vision to include such diverse factors as the homes people come from, the effects of competition for living space and privacy, the means of paying for health care, and the resources for health ser-

The "Partnership for Health" legislation that launched comprehensive health planning directs the health planners to involve large segments of community leadership. The law says the planners are not only those who call themselves planners, but also the representatives of the people and groups being planned for. Many who have not before considered themselves planners are asked to share the responsibility for planning.

This means the physician, the dentist, the optometrist, the hospital administrator—those who have been and in the future will be concerned with the provision of care. It also means insurance companies and educators, voluntary health associations and professional societies. Others, like the armed services, whose provision of care for servicemen and dependents is a vast enterprise, should be asked to participate in the planning.

The State Department of Public Health, as the state planning agency under Public Law 89-749, is assigned the responsibility to begin planning not only for its own operations, but for the statewide comprehensive health planning program. The Department has proceeded with a certain amount of caution and flexibility, because the first activities must include as many as possible of those persons with whom we share the responsibility for planning.

The designation of Planning Agency does not

suddenly relieve others of their responsibilities to maintain and improve their programs of health care. The Department can assist in some of the information and provide some of the materials useful for better planning.

The special knowledge of particular fields, such as the treatment of stroke or the effects of overcrowding on the mental health of the people in urban areas, must be provided by those who have the background and experience to measure and develop programs of services. The Department hopes to provide a forum and a format for planning.

Planning can be defined in many ways. There is planning for resources and planning for services. There is planning for the environment and planning for persons who have not shared in the full benefits of modern medicine. Planning at the state level is essentially a process of identifying alternative approaches to health problems, and permitting choice of the alternatives. There are limits to our capabilities and there must be a mobilization of the community to assure that the limited resources are utilized most effectively on the most important problems.

Because some problems extend beyond community boundaries, or community resources may be insufficient to resolve a problem, there is a need for area-wide coordination of local planning for action. The partnership begins to establish a framework for planning which recognizes the relationships of providers and users, community needs and resources, area-wide problems and statewide goals.

This framework provides the basis for decisions on limits to be prescribed for planning efforts. This process permits judgment by the State Planning Agency and the State Health Planning Council on the direction and achievements of action programs.

The interchange between the various positions within this framework for planning must be continuous and cooperative to create an effective partnership. Most of us have engaged in planning to some degree. Mostly we have planned a way to do a specific thing. We are now being given the opportunity to participate with many others in planning for comprehensive health.

*A new Director for the Department, Louis F. Saylor, M.D., was named 27 June.



Atrial Septal Defect— Ostium Secundum Variety

A Review of 117 Cases

RAFAEL RODRIGUEZ, M.D., AND WILLIAM J. KUZMAN, M.D., *San Diego*

■ *Atrial septal defect is one of the most common congenital cardiac lesions seen at most centers. Typically one notes on physical examination a pulmonic lift with associated right ventricular lift. Wide splitting of the second sound is associated with a Grade II to III systolic pulmonary ejection murmur. Characteristically, the electrocardiograph discloses an incomplete or complete right bundle branch block.*

This lesion is often well tolerated into the third and fourth decades of life. Subsequently one notes progressive cardiac symptomatology and eventual inoperability due to fixed pulmonary vascular changes.

Our experience would indicate this entity to be readily correctable with an extremely low morbidity and mortality. Good result can be anticipated in all age groups.

ATRIAL SEPTAL DEFECT of the ostium secundum variety is one of the most common forms of congenital heart disease. A review of all charts at the San Diego County Heart Center, from 1955 to 1965, disclosed this defect to be present in 117 of 821 patients, an incidence of 14.3 percent. This congenital defect was demonstrated by catheterization in 101 patients and anatomically at operation in 83. In the remaining 16 cases the diagnosis was established on clinical grounds only.

It should be noted 29 of the 117 patients had

pulmonary hypertension. Associated partial anomalous pulmonary venous drainage was present in 19 patients. Twelve patients also demonstrated a gradient across the infundibular portion of the right ventricle. In all of these patients the peak systolic gradient was less than 30 mm of mercury and was considered to be a flow gradient. These patients form the basis of this clinical report.

During the ten-year period spanned by this report, six patients died, five postoperatively and one in severe congestive failure. The following report will concern itself with various clinical, electrocardiographic, radiographic and physiological parameters in these patients as well as an analysis of the surgical results.

From the San Diego County Heart Center at The Donald N. Sharp Memorial Community Hospital. This study was supported by the San Diego County Heart Association.

Reprint requests to: Cardio-Respiratory Center, The Donald N. Sharp Memorial Community Hospital, 7901 Frost Street, San Diego 92123 (Dr. Kuzman).

Age and Sex

Patients ranged in age from 11 months to 69 years. The largest number of patients (56) were seen in the first decade of life. Females outnumbered males by almost two to one. This high sex incidence of atrial septal defects in females has been commented upon by other observers.^{1,2}

Symptoms

The majority of patients (78.4 percent) were asymptomatic. These patients were referred for evaluation of a murmur, generally detected on routine school examination or during the course of respiratory tract infection.

In the symptomatic patients the main complaint was of dyspnea, mainly on exertion. The presence and severity of dyspnea clearly increased with age beginning with the second decade (Chart 1). A correlation was noted also between dyspnea, age and the development of pulmonary hypertension (Chart 2).

Clinically it was of interest to note that all patients in the first decade of life were totally asymptomatic although nine of them had elevated pulmonary artery pressure. With advancing age, the development of clinical symptoms became more commonplace until, in the sixth and seventh decades, all patients were noted to be symptomatic. It is in this group of patients that the diagnosis of atrial septal defect becomes clinically difficult and the condition is often confused with rheumatic heart disease.³ The presence of associated coronary artery disease may well be a factor in the production of symptoms in the older age group.

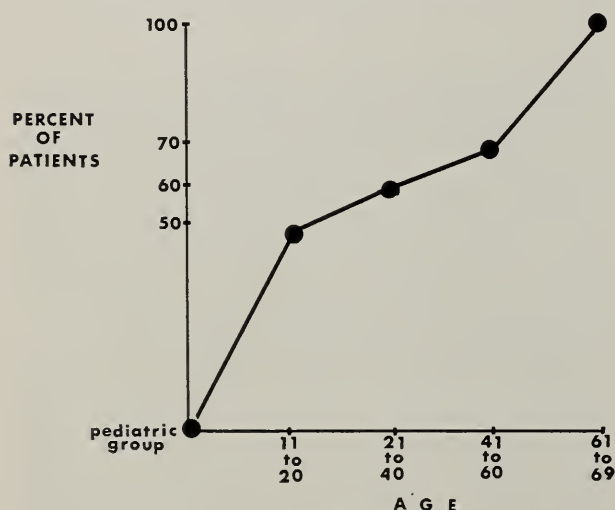


Chart 1.—Relationship between age and dyspnea. Note the majority of patients in fifth to seventh decade were symptomatic.

Physical Findings

Precordial asymmetry was detected in 25 percent of the patients. Inspection also disclosed the presence of clubbing and cyanosis in four patients. In all of these patients the pulmonary vascular obstructive syndrome⁴ had developed.

Palpation disclosed the presence of a pulmonic lift in the majority. Pulmonary closure tap and right ventricular lifts were also frequent findings, especially in young patients with moderate to large shunts. With advancing age the presence of a pulmonary closure tap or right ventricular lift strongly suggested the presence of anatomical changes within the right ventricle or pulmonary vascular bed. The presence of all three physical findings in the same patient signified the presence of a large left to right shunt complicated by moderate to severe pulmonary hypertension. A systolic thrill was a rare finding in uncomplicated atrial septal defects but was noted in seven of twelve patients with associated pulmonary stenosis. The presence of a thrill bore no relation to the severity of the stenosis.

On auscultation wide splitting of the second sound at the second left intercostal space was noted in 75 percent of the patients. P2 was equal to or louder than A2 in the majority of patients and the degree of splitting was considered fixed in most. In patients with pulmonary hypertension the second sound at the pulmonic area was always accentuated. Close splitting occurred except in patients with concomitant complete right bundle branch block. This will be discussed further under phonocardiography.

A systolic murmur of Grade II to III intensity on a basis of 0 to VI was heard in the majority of patients with uncomplicated atrial septal defects. This murmur was maximal at the second left intercostal space and transmitted as a rule into the left infraclavicular area and through to the left chest

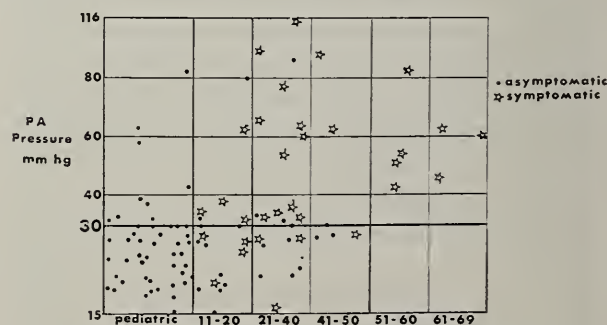


Chart 2.—Relationship between symptoms, age, and systolic pulmonary pressures showed a direct correlation.

posteriorly. In a few patients the murmur was of maximal intensity in the third left intercostal space. A systolic murmur of tricuspid insufficiency was heard at the fourth left intercostal space in the older group whose clinical course was complicated by congestive failure. Diastolic murmurs of pulmonic insufficiency were noted in only seven patients and bore no relation to the presence of anomalous pulmonary venous return or pulmonary hypertension but was related to the size of the shunt. A diastolic murmur of relative tricuspid stenosis was heard in 60 patients. There was good correlation between this murmur and the degree of left to right shunt.

Phonocardiography

Phonocardiograms were available in 46 patients. The time interval from the onset of ventricular depolarization to the first significant component of the first heart sound (Q-M1 interval) ranged from 40 to 90 milliseconds (msec). An early systolic ejection click was recorded in six instances.

A systolic ejection murmur of varying intensity and duration was recorded in every case. This murmur was most prominent over the pulmonic area. In seven cases a diastolic murmur of pulmonic insufficiency was also evident.

The second heart sound at the pulmonic area has assumed prime importance in the diagnosis of congenital heart disease and was carefully evaluated in all patients. In the majority of patients (87 percent) the aortic and pulmonic components of the second sound were widely split from 40 to 60 msec, with a range from 20 to 80 msec.

In patients in whom pulmonary hypertension developed, close splitting of the aortic and pulmonic components was noted. One patient with wide splitting and pulmonary hypertension had a complete right bundle branch block.

These findings would tend to confirm the clinical impression that electrical and mechanical events govern the degree of splitting of the second sound. As pulmonary hypertension develops, closure time of the pulmonic component shortens with P2 approaching A2 unless counterbalanced by the pronounced delay in electrical depolarization of the right ventricle as seen in complete right bundle branch block.

The amplitude of the pulmonic component of the second sound generally exceeded the aortic component and clearly increased in amplitude

when the pressures in the pulmonary circulation were elevated.

In seven patients with gradients across the pulmonary valve it was noted that the interval between A2 and P2 varied directly with the gradient across the valve. This has been further documented in our large series of patients with pure pulmonary stenosis and is believed to relate to the prolonged mechanical ejection time of the right ventricle. The pulmonic component in patients with pulmonary stenosis was always diminished in contrast to the aortic sound.

Roentgenographic Features

The overall heart size was considered normal in 42 percent of the 117 patients. In 32 percent of the cases mild to moderate cardiomegaly was present and there was gross cardiac enlargement in 26 percent. In uncomplicated atrial septal defects 80 percent of the patients had normal heart size (Chart 3). When anomalous pulmonary venous return of pulmonary hypertension complicated the presence of an atrial septal defect, moderate to gross cardiomegaly was a common associated finding. Direct correlation was noted between the presence of anomalous pulmonary venous return, pulmonary hypertension, age of the patient and the presence of cardiomegaly. No patient beyond the fifth decade of life had a normal sized heart.

Prominent main pulmonary artery segment and increased pulmonary vascularity were also frequent findings, and the incidence of these conditions is summarized in Chart 3.

Electrocardiographic Findings

The basic hemodynamic alteration in atrial septal defects is the presence of an abnormal flow of

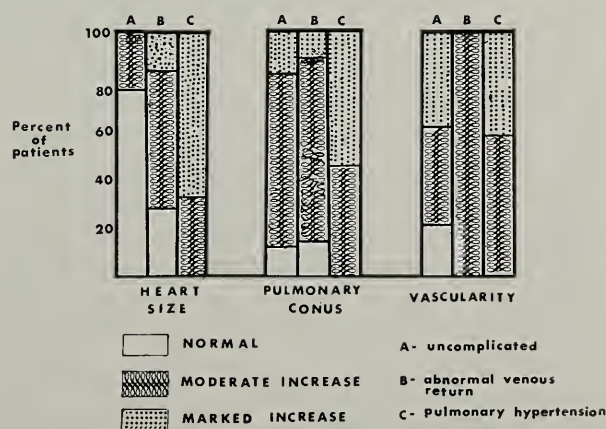


Chart 3.—Roentgenographic findings in various categories of patients. See text for discussion.

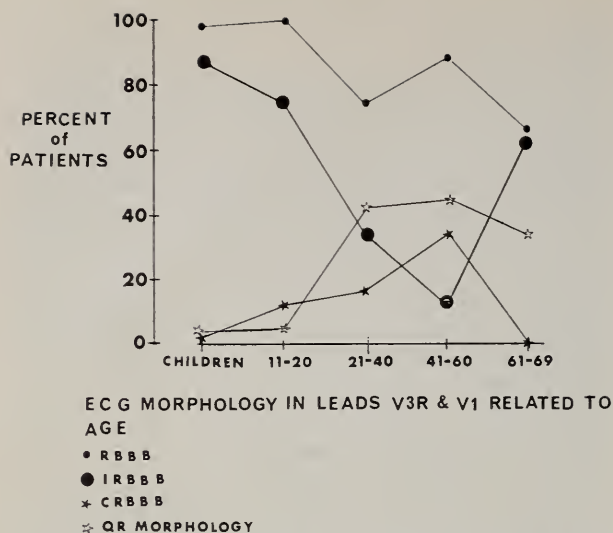
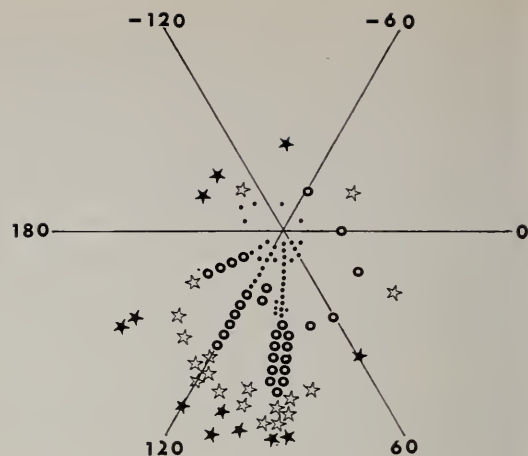


Chart 4.—ECG morphology in leads V3R and V1 related to age:
 RBBB—right bundle branch block.
 IRBBB—incomplete right bundle branch block.
 CRBBB—complete right bundle branch block.

blood across the atrial septum, producing a diastolic overload of the right ventricle. The right ventricle under these circumstances must adapt by initial dilatation and subsequent hypertrophy. The anatomical changes generated by the hemodynamic alteration are probably instrumental in causing the delay in electrical conduction so frequently seen in this entity. In 91 percent of our patients a complete or incomplete right bundle branch block pattern was demonstrated. In the first two decades the incidence was 100 percent (Chart 4) and declined slightly in subsequent decades, reaching 64 percent in the seventh decade. The inscription of morphologic features of right bundle branch block was evident in the form of incomplete or complete right bundle branch block and QR complexes with decided slurring of the R wave in the right precordial leads in 8 of the 101 patients with proven defects. Similarly, we recorded slurring of the S waves in lead 1 and left precordial leads in an additional five cases, with the typical R-R¹ pattern in the right precordial leads. It can be seen that the high incidence of incomplete right bundle branch block found in the pediatric age group declines progressively as age advances and conversely complete right bundle branch block and QR morphologies develop with increasing age. These findings tend to suggest that as the degree of block increases with age, it is associated with progressive dilatation of the right ventricle.

Similarly the development of QR morphologic features in V1 most likely represents progressive



- uncomplicated
- P.H.
- ☆ A.V.R.
- ★ P.S.

Chart 5.—Electrical axis plotted on Bayley's triaxial reference frame.

P.H.=pulmonary hypertension
 A.V.R.=anomalous venous return
 P.S.=pulmonary stenosis

right atrial dilatation. The electrical axis in the majority of patients was placed to the right between plus 90° to plus 150°. In a few cases the electrical axis was in the second or third sextant of Bayley with an S1, 2, 3 pattern in the standard leads to indicate posterior displacement of the apex of the heart (Chart 5). There is a tendency to deviate the electrical axis toward the left in the older age group and this may relate to the presence of coronary artery disease in this age group. This leftward deviation, however, was more frequently counterbalanced by the developing pulmonary hypertension with a subsequent systolic overload of the right ventricle.

Hemodynamic Findings

During the period 1955 to 1965, conventional right heart catheterization was carried out 113 times in the 101 patients. In three patients in whom mitral insufficiency complicated the atrial septal defect, left heart study was also carried out. Catheterization was carried out under local anesthesia, with the basilic vein utilized in most instances. The brachial artery was also cannulized with a Courmand needle percutaneously at the time of study.

There were no serious complications associated with the procedure and no deaths occurred. In many patients transitory arrhythmia was recorded

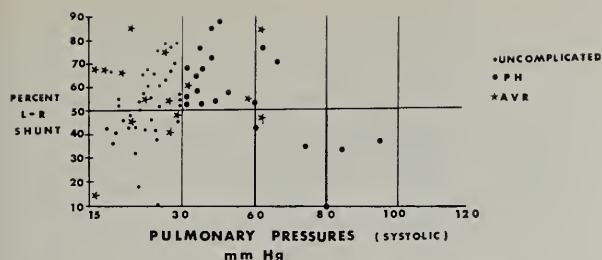


Chart 6.—Relationship between the magnitude of the left to right shunt and pulmonary artery pressures. Size of shunt is diminished as systemic levels are approached.

during the course of catheter manipulation but no prolonged supraventricular or ventricular tachycardia was encountered. In adults, vaso-vagal reactions with bradycardia and nausea were commonplace despite atropinization prophylactically.

Double scale oximetry and Van Slyke determinations⁵ were carried out in all cases with multiple specimens obtained from the right heart chambers. A minimum of three specimens were obtained from the various sampling sites. In all patients, except one with reversed shunt, a significant step-up in saturation was noted at the right atrial level. From 1963 on, hydrogen curves were recorded in conjunction with conventional techniques and this has been a most valuable adjunctive measure. In 88 percent of the patients, an unidirectional shunt was demonstrated. However, in 12 percent some degree of right to left

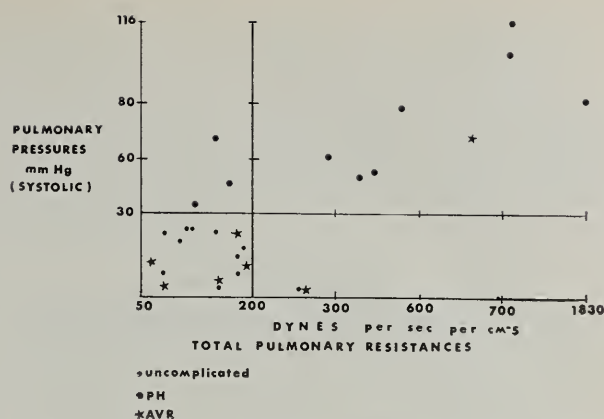


Chart 7.—Correlation between systolic pulmonary pressures and total pulmonary resistances demonstrates direct correlation but exceptions are noted. See text for discussion.

shunting was present. A predominant left to right shunt was noted even in patients with pulmonary hypertension, with the exception of one instance of typical pulmonary vascular obstructive syndrome. Pathological findings in this patient included Grade IV diffuse intimal and medial changes as described by Heath and Edwards.⁶ The magnitude of the left to right shunt was calculated according to conventional formula and the degree of shunting was expressed as percent of pulmonary blood flow. The left to right shunts ranged from 10 to 85 percent of the pulmonary blood flow, with the majority above 50 percent. There

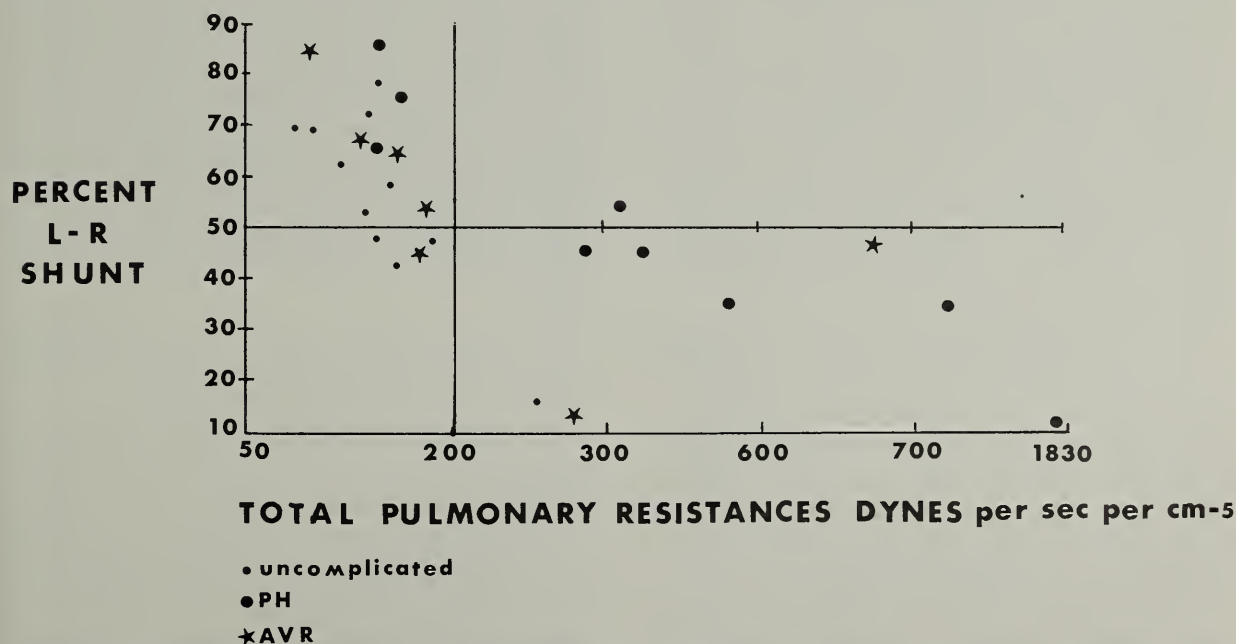


Chart 8.—Plot between percent left to right shunt and total pulmonary resistances. As resistance increases, the magnitude of shunt diminishes.

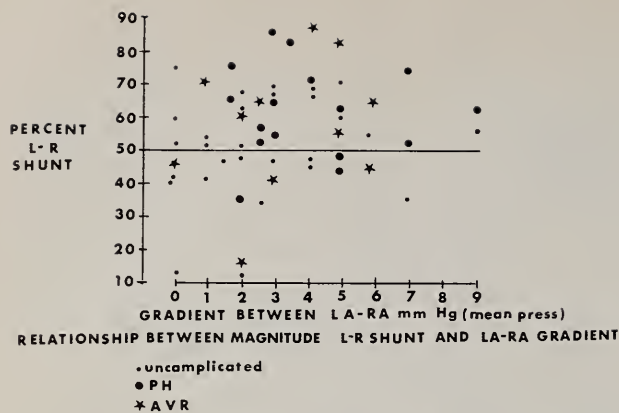


Chart 9.—Comparison between left atrial and right atrial gradient and percent of left to right shunt bore no constant relationship.

was no difference between simple atrial septal defects or those complicated by anomalous pulmonary venous drainage or mild to moderate pulmonary hypertension with respect to the degree of shunting (Chart 6). When severe pulmonary hypertension occurred (more than 75 mm of mercury systolic), left to right shunting decreased and the incidence of bi-directional shunting increased. These findings support the generally held impressions that the magnitude of left to right shunt is inversely related to the magnitude of the pulmonary artery pressure when the pressure is decidedly elevated and associated with moderate to severe increase in pulmonary vascular resistances.

It is in this group that elevated pressure is believed to represent secondary changes reflecting the development of pulmonary arterial changes with increased pulmonary resistances (Chart 7). The right ventricle responds to this increased systolic overload by developing right ventricular hypertrophy. The latter is associated with decreased compliance and reduced distensibility with increased resistance to diastolic filling, which reduces accordingly the degree of left to right shunt (Chart 8).

In the present study 62.4 percent of patients had normal pulmonary artery pressure and pulmonary hypertension was present in 37.6 percent. In the pediatric age group slight to moderate pulmonary hypertension occurred in 10.8 percent. However, in only one patient was severe elevation of pressure recorded. These findings indicate that despite large left to right shunts at the atrial level, flow *per se* is not sufficient to produce pulmonary hypertension. The readily distensible pulmonary vascular bed can respond to increased flow by opening additional channels to accommodate the

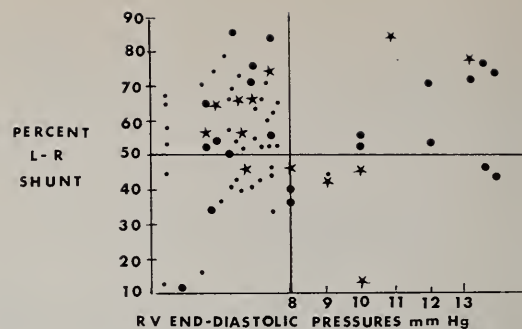


Chart 10.—Magnitude of left to right shunt plotted against right ventricular end-diastolic pressure failed to demonstrate a positive or negative correlation.

additional flow. We also analyzed the possible relationship between the magnitude of the left to right shunt and the mean gradient between the two atria and noted no correlation (Chart 9). Analysis of the end-diastolic pressure within the right ventricle in similar context failed to disclose any positive relationship (Chart 10).

Cardiac output was determined by the Fick method in 27 patients. In 48 percent the systemic cardiac index was below normal (2.50 to 3.75 liters per minute per square meter of body surface). In 37 percent it was normal and in 15 percent it exceeded normal.

Surgical Treatment

During the period from 1955 to 1964, 83 patients were operated on for correction of atrial septal defects along with any significant associated defects. Most of the operations (69.8 percent) were done at the Donald N. Sharp Memorial Hospital. The selection of patients for operation was based on careful clinical assessment and the degree of hemodynamic alteration at the time of cardiac catheterization. In two cases operation was decided against because of advanced pulmonary vascular changes.

In the early years of surgical correction, hypothermia was employed; later, extracorporeal circulation became the procedure of choice.

At the time of operation a septal defect of ostium secundum type was found in each instance. The defect varied in size from 2 cm to as large as 5 cm. In the majority it was between 2.5 and 3 cm. Distention of the right heart structures was noted frequently at operation, with the main pulmonary artery larger than the aorta as a rule. In general, the large defects were associated with large left to right shunts.

Anomalous pulmonary venous drainage commonly involved the right lung. These veins drained into the superior vena cava or right atrium. In one patient the entire right lung drained into the inferior vena cava. In another the inferior vena cava emptied into the left atrium—so-called cyanotic atrial septal defect without pulmonary hypertension.⁷

After operation the patients made uneventful recovery, with decrease in heart size, loss of murmurs and improvement in exercise tolerance. Radiographically, dilation of the main pulmonary artery persisted. Electrocardiographically, patients with prominent right ventricular hypertrophy showed improvement, although varying degrees of right bundle branch block persisted.

There were five surgical deaths recorded (6 percent). One of the patients who died was of the uncomplicated group, and death in that case

was associated with massive postoperative pulmonary and cerebral thrombosis. In the complicated group, there were three immediate postoperative deaths and one late death. These four patients all had severe pulmonary hypertension and in one a disturbing underdeveloped left ventricle was observed at autopsy.

REFERENCES

1. Zaver, A. G., and Nadas, A. A.: Atrial Septal Defect Secundum Type, *Circulation*, Vol. 32, Supplement III, 24, 1965.
2. Abbott, M. E.: *Atlas of Congenital Heart Disease*, American Heart Association, New York, 1936.
3. Kuzman, W. J., and Yuskis, A. S.: Atrial septal defect in the older patient simulating acquired heart disease, *Amer. J. Cardiol.*, 15: 303, 1965.
4. Cuder, J. G., Nadas, A. S., Goodale, W. T., Hickler, R. B., and Rudolph, A.M.: Pulmonary arterial hypertension with markedly increased pulmonary resistance, *Am. J. Med.*, 17:485, 1954.
5. Van Slyke, D. D., and Neill, J.M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement, *J. Biol. Chem.*, 61:523, 1924.
6. Heath, D., and Edwards, J. E.: The pathology of hypertensive pulmonary vascular disease: A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects, *Circulation*, 18:533, 1958.
7. Wood, P.: *Diseases of the Heart and Circulation*, 2 Ed., J. B. Lippincott Company, Philadelphia, 1956.

SUBACUTE BACTERIAL ENDOCARDITIS WITHOUT A MURMUR

"Until about seven or eight years ago, I was happy to accept that patients who did not have a cardiac murmur could not have subacute bacterial endocarditis. I can tell you now that this is not true. We have collected up to this point ten patients who have had SBE—a couple of whom had to go to the pathologist to have the diagnosis made—who at no time had any murmur. SBE may run its entire course and leave no murmur. In some instances, the patient has no murmur when he starts his disease, but has one reflecting the valve that's involved by the time he finishes his treatment and is followed over a period of several months. One-third of patients with SBE do not have a significant cardiac murmur at the time they are first seen for this disease; and, if they don't rupture a valve leaflet, may run their entire course without developing a murmur—this being heard only weeks or months after recovery has taken place. The same thing is true of right-sided endocarditis . . ."

—LOUIS WEINSTEIN, M.D., Boston
Audio-Digest *General Practice*, Vol. 16, No. 11

Screening for Bacteriuria by the Miniature Culture Technique

ROBERT L. DUNCANSON, M.D., AND JOSEPH W. ST. GEME, JR., M.D. *Torrance*

■ *Two hundred and eighteen urine specimens were cultured in duplicate to compare the reliability of a miniature culture technique with a more standard, calibrated loop-method for quantitative urinary bacteriology. The new method appears to be reliable: the rate of false negative results was 2.5 percent and of false positive 3.6 percent. The correlation with the standard method was best in the ranges of 0 to 10,000 and greater than 100,000 colonies per milliliter. The technique is simple, quick, and easily applicable to the physician's office laboratory.*

THE VITAL IMPORTANCE of quantitative urine cultures in the definitive diagnosis of urinary tract infections was first demonstrated by Marple¹² in 1941. The observation by Kass⁶ in 1955 that 100,000 colonies of bacteria per ml of urine constituted a significant infection led to the widespread use of quantitative urine cultures by clinicians.

At the present time it is generally accepted that a urine culture with less than 10,000 colonies per milliliter suggests artefactual contamination, while a pure culture of more than 100,000 colonies denotes significant bacilluria. The intermediate zone of 10,000 to 100,000 colonies per milliliter remains indeterminate and requires repeated investigation.^{7,8}

The standard method for quantitating bacteriuria has involved the use of pour-plates, requiring serial dilutions of urine, but the increased demand for accurate, quantitative urine cultures has en-

couraged laboratories to seek quicker, more economical methods.

One of the currently popular alternate methods, first described by Hoeprich,⁴ involves the inoculation of agar plates with undiluted urine, using a loop calibrated to deliver a specific volume of 0.001 ml. Hoeprich demonstrated an excellent correlation with the standard pour-plate technique. The reliability of the loop technique has been confirmed by Shaw and coworkers.¹⁷ A modification of this method, using a loop delivering 0.01 ml rather than 0.001 ml, has also been described.⁴ At present over 80 percent of the major hospital laboratories in the Los Angeles area have adopted some modification of the loop technique for their routine quantitative urine cultures.

Kunin and others^{9,10} demonstrated an impressive incidence of asymptomatic bacteriuria in school children. While this incidence is low in boys (0.04 percent), it may be as high as 1.2 percent in girls, and frequently is associated with significant urinary tract anomalies. It may be hoped that early detection of such conditions would minimize ultimate renal damage. Therefore an accurate method for simple screening of urine

From the Department of Pediatrics, UCLA School of Medicine at Harbor General Hospital, Torrance.

Submitted 31 Aug. 1967.

Reprint requests to: C/o 2845th USAF Hospital, Griffiss AFB, Rome, New York 13440 (Captain Robert L. Duncanson, MC, USAF).



Figure 1.—The two methods of culture used in the present study. A standard 9 cm Petri-dish containing EMB agar shows the bacterial growth from two urine specimens (see text). Below the dish, the 0.001 ml calibrated loop is also illustrated. The four miniature culture plates demonstrate significant and insignificant growth (see text) with the filter paper dip-stick shown above them.

samples for bacilluria would be of great value.

Microscopic examination of the urinary sediment is a reliable method for detecting pyuria. However, several studies^{5,14} have clearly demonstrated that the absence of pyuria does not rule out significant bacteriuria and that microscopically "clear" urine may be obtained from patients with symptomatic urinary tract infections. Therefore, microscopic urinalysis alone is a poor screening method for the detection of bacteriuria.

Other rapid methods, introduced widely during the past five years, have relied upon the biochemical alteration of various reagents by the metabolic by-products of respiring bacteria. Because of inordinately numerous false negative results, both the triphenyl tetrazolium chloride (TTC) test and the Griess test are inadequate for routine screening purposes.^{1,2,13,16}

Many practicing clinicians obtain and evaluate

throat cultures in their office laboratories, but rarely undertake routine culture of the urine, despite the relative simplicity of the loop technique.

A new screening method, employing miniature agar plates, is now available* and recently has been favorably evaluated by Hobday.³ It was the purpose of this study to verify and extend the reliability of this new method, and to compare it simultaneously with the loop technique.

Method

Aliquots were removed from 218 urine specimens, taken at random from over 1,000 specimens submitted to the Harbor General Hospital bacteriology laboratory during a period of two months. Standard clean-catch, mid-stream urine specimens are obtained for routine culture in this hospital. Each specimen was refrigerated within 30 minutes of collection, and cultured by each method within 12 hours.

Standard System: A platinum loop, calibrated by the manufacturer† to deliver 0.001 ml (Figure 1), was used to inoculate both eosin-methylene-blue (EMB) and sodium-azide blood agar plates.¹⁷ The cultures were incubated overnight at 37°C and the number of colonies counted. The recorded value, in colonies per milliliter, is 1,000 times the number of colonies observed on the plate, consistent with the original urine volume of 0.001 ml. Results were tabulated as: 0 to 10,000 cols/ml; 10,000 to 100,000 cols/ml; and greater than 100,000 cols/ml. Figure 1 also illustrates a standard EMB plate which, following inoculation and incubation of two separate urine specimens, reveals *E. coli* in concentrations greater than 100,000 cols/ml. The upper half, with nearly solid bacterial growth along the lines of inoculation, represents a bacterial concentration far in excess of 100,000 cols/ml. The colonies on the lower half can be more carefully counted and represent a concentration of approximately 325,000 cols/ml.

Test System: The miniature-culture system, described in detail by Hobday,³ consists of shallow rectangular plates (1.3 x 2.0 cm) containing trypticase soy agar culture medium. The plates are inoculated, using specially-perforated sterile strips of filter paper that is dipped into the urine to the perforated mark, then applied directly onto the agar surface with gentle pressure for 10 seconds.

* Available as "Testuria," from Ayerst Laboratories.

† Available from Scientific Prod., 3815 Valhalla Dr., Burbank, Calif. Cat. No. N-2075-2.

TABLE 1.—Correlation of results of 218 urine cultures using the calibrated loop and miniature culture techniques.

CALIBRATED LOOP (colonies/ml)	MINIATURE CULTURE (colonies/plate)			Totals	Percent Correlation
	0-2 ¹	3-25 ²	26+ ³		
0-10,000	135	5	—	140	96.4
10,000-100,000	2	14	3	19	73.7
100,000	—	—	59	59	100.0
Totals	137	19	62	218	

¹Negative.

²Suspicious.

³Positive.

The culture is resealed and incubated overnight.

The pharmaceutical directive considers 0 to 2 colonies per plate as a negative culture, 3 to 25 colonies as questionable, and 26 or more colonies as positive. These limits were used in reading the plates in this study, and examples are shown, (bottom of Figure 1 from left to right) of confluent growth (too numerous to count), 38 colonies, 2 colonies, and no growth on the plates.

Results

Table 1 shows the correlation between quantitative cultures using the standard loop and the miniature culture techniques. All 59 specimens found to contain more than 100,000 cols/ml by the standard loop technique were also detected by the miniature culture technique. Two of the additional three specimens interpreted as significantly positive on the miniature plate produced growth in the range of 80,000-95,000 by the loop method. Similarly, at the other end of the spectrum, both specimens interpreted as "negative" by miniature culture, but "suspicious" by loop, have quantitative colony counts of 11,000 and 12,000 per ml. The percentage of correct correlation within each group is also shown in the table, the least accurate being in the indefinite "suspicious" zone of 10,000 to 100,000 cols/ml.

If only bacteriuria exceeding 100,000 cols/ml is considered significant, there were no false negative results using the miniature culture technique. However, when cultures yielding 10,000 to 100,000 cols/ml are considered, two of seventy-eight cultures would have been interpreted as negative by the miniature culture technique, or a 2.5 percent incidence of false negative results.

Similarly, none of the 140 cultures negative by loop technique would have been considered significantly positive on the miniature cultures; but five of the miniature cultures were interpreted as

suspicious—a 3.6 percent incidence of false positive results.

These figures are comparable with or slightly more favorable than those reported by Hobday.³

Discussion

The miniature-culture technique has been developed following the observations of Ryan and coworkers¹⁵ in 1962. These investigators pointed out that strips of filter paper of known dimension could be used to transfer organisms from liquid to solid media. The number of organisms transferred depends primarily on the concentration of organisms present in the liquid media. Other minor factors include the porosity and absorbent qualities of the filter paper, the length of time between dipping the paper and applying it to the agar surface, and the length of time the strip is held in contact with the agar.

Leigh and Williams¹¹ developed calibration curves using known concentrations of each of several microorganisms. Their data indicated that 25 colonies of Gram-negative bacilli per miniature plate correlated best with 100,000 cols/ml. When streptococcal species were studied the significant colony count was 30.

Hobday³ did not explain why in his studies a plate count of five or more colonies was considered significantly positive. Our data suggest that the manufacturer's recommendations, based on Leigh and Williams' observations, are more compatible with the usually accepted limits of significant and insignificant bacteriuria.

The correlation between the standard calibrated loop and the miniature culture technique seems to be excellent. The method is simple and requires no additional materials, equipment (beyond incubator) or unusual skill. At current prices the unit cost (40 cents) approximates that of a prepared blood agar plate as commonly used for throat cultures.

When significant growth is observed on the miniature plate, positive identification and sensitivity testing can be pursued only after subculturing colonies on appropriate solid media. In contrast the simultaneous use of blood agar and EMB plates in the loop technique permits positive identification of the organism in 60 to 70 percent of cultures simply by colonial morphology.¹⁷ For these reasons, the new method is unlikely to replace the calibrated loop in hospital laboratories. However, for the practicing clinician, who would be unlikely

to undertake specific fermentative studies in his office laboratory, this should pose no major disadvantage. The sealed plate can simply be sent to a laboratory for routine subcultivation.

The manner by which asymptomatic bacteriuria should be managed falls beyond the scope of this paper, but certainly widespread screening of well children for bacilluria would at least detect cases in which further evaluation is needed. Thus unrecognized asymptomatic urinary tract anomalies or simple infections can be recognized sooner and treated before irreversible renal damage has occurred. The miniature culture technique provides a practical solution for simple and accurate screening of urine samples in the clinic setting.

REFERENCES

1. Bulger, R. J., and Kirby, W. M.: Simple tests for significant bacteriuria, *Arch. Int. Med.*, 112:742, Nov. 1963.
2. Hirach, H. A., and Blay, E.: Comparison of several methods of quantitative bacterial urinalysis; *From Progress in Pyelonephritis*, E. H. Kass, Ed., F. A. Davis Co., Philadelphia, 1965, pp. 550-557.

3. Hobday, J. D.: A simplified culture method for detecting asymptomatic bacteriuria in children, *Peds.*, 38:903, Nov. 1966.
4. Hoeprich, P. D.: Culture of the urine, *J. Lab. & Clin. Med.*, 56:899, Dec. 1960.
5. Hoeprich, P. D.: Correlation of culture and sediment findings in urinary tract infections, *J. Clin. Invest.*, 40:1049, 1961.
6. Kass, E. H.: Asymptomatic infections of the urinary tract, *Trans. Ass. Amer. Physicians*, 69:56, 1956.
7. Kass, E. H.: Bacteriuria and pathogenesis of pyelonephritis, *Lab. Invest.*, 9:110, 1960.
8. Kass, E. H.: Pyelonephritis and bacteriuria, *Ann. Int. Med.* 56:46, Jan. 1962.
9. Kunin, C. M., Zacha, E., and Paquin, Jr., A. J.: Urinary tract infections in school children, *N.E.J.M.*, 266:1287, June 1962.
10. Kunin, C. M. and Paquin, Jr., A. J.: Frequency and natural history of urinary tract infections in school children; *From Progress in Pyelonephritis*, E. H. Kass, Ed., F. A. Davis Co., Philadelphia, 1965, pp. 33-44.
11. Leigh, D. A., and Williams, J. D.: Method for the detection of significant bacteriuria in large groups of patients, *J. Clin. Path.*, 17:498, July 1964.
12. Marple, C. D.: The frequency and character of urinary tract infections in an unselected group of women, *Ann. Int. Med.*, 14:2220, June 1941.
13. Netter, E.: Evaluation of tetrazolium test for diagnosis of significant bacteriuria, *JAMA*, 192:769, 31 May 1965.
14. Pyles, C. V., and Elliot, C. R.: Pyuria and bacteriuria in infants and children, *Am. J. Dis. Child.*, 110:628, Dec. 1965.
15. Ryan, W. L., Hoody, S., and Luby, R.: A simple quantitative test for bacteriuria, *J. Urol.*, 88:838, Dec. 1962.
16. Sacks, T. G., and Abramson, J. H.: Screening tests for bacteriuria, *JAMA*, 201:1, July 1967.
17. Shaw, Jr., S. T., Hopp, M., and St. Geme, Jr., J. W.: Quantitative urine culture with calibrated bacteriologic loop, *Minn. Med.*, 49:749, May 1966.

A DISMAYING USE OF DRUGS BY YOUNGSTERS

"We as physicians seem unable to cope with today's youngsters and their drugs. There are so many cultural, sociologic, educational and legal ramifications to the problem that merely sitting in our offices and prescribing antidotes for the various drugs used—employing the medical model—is totally inadequate, for these teenagers are 'turning on' with new drugs all the time. They are smoking wheat, lettuce, and crushed aspirin. They are ingesting diluted Murine eyewash, Asthmador, Ban deodorant, and Clinitest tablets. And they are injecting Accent meat tenderizer, to name just a few. . . . So many of the youngsters who end up injecting methedrine began by ingesting their mothers' medically-prescribed amphetamine diet pills. Many first began on the barbiturates by taking their parents' medically-prescribed sleeping pills. Let's face it: we physicians are very directly involved in what's going on with youth and drugs and, certainly, we must accept some of the responsibility."

—THOMAS UNGERLEIDER, M.D., Los Angeles
Audio-Digest *General Practice*, Vol. 16. No. 18

Osteoarthritis of the First Carpometacarpal Joint

J. B. PETER, M.D., PH.D., AND LEONARD MARMOR, M.D., *Los Angeles*

■ *The first carpometacarpal (trapeziometacarpal) joints are a frequent site of osteoarthritis in postmenopausal women. This osteoarthritis, which is typically bilateral both clinically and roentgenographically, may be mistaken for tenosynovitis unless its characteristic features are recognized. These features include tenderness, stiffness, crepitus, swelling, and pain on wringing movements or other motions that cause abduction of the thumb. The swelling, radial subluxation of the metacarpal and atrophy of the thenar muscles give the hand a squared appearance.*

In severe cases, conservative medical therapy is generally unsatisfactory. Intra-articular corticosteroids and local anesthetic give only transient relief. Results of surgical therapy, including excision of the trapezium or arthrodesis of the trapeziometacarpal joint, were in general good. Distinct indications exist for each type of operation.

FAILURE TO RECOGNIZE that the first carpometacarpal (trapeziometacarpal) joints are frequently damaged by osteoarthritis often leads to erroneous diagnosis. In addition, because little has been written about osteoarthritis of this joint, the modes of therapy are not well known. It is the purpose of this paper to review the features of first carpometacarpal osteoarthritis and to comment on the medical and surgical treatment.

Clinical Features

In our experience osteoarthritis of the first carpometacarpal joint is probably second in fre-

quency only to Heberden's and Bouchard's nodes, which are the osteophytes associated with osteoarthritis of the distal and proximal interphalangeal joints of the hands (Figure 1). First carpometacarpal osteoarthritis has not been sufficiently emphasized and this may account in part for the widespread failure to recognize the manifestations of this disease.

The disorder can occur without other clinical evidence of osteoarthritis, with Bouchard's and/or Heberden's nodes alone, with generalized osteoarthritis or with erosive osteoarthritis. Regardless of the general clinical condition, the manifestations of osteoarthritis in this joint are usually quite distinctive. There is tenderness on palpation of the joint together with stiffness and pain. The pain, which is sometimes severe and incapacitating, may

From the Departments of Medicine/Rheumatology (Peter) and Surgery/Orthopedics (Marmor), U.C.L.A. School of Medicine.
Submitted 19 Oct. 1967.

Reprint requests to: Department of Medicine, U.C.L.A. School of Medicine, Los Angeles 90024 (Dr. Peter).



Figure 1.—Heberden's and Bouchard's nodes.

be confused with extensor or abductor tenosynovitis (de Quervain's disease) and less frequently with flexor tenosynovitis. Crepitus is noted when the metacarpal is rotated on the trapezium (greater multangular). Swelling over the joint may be mistaken for a ganglion but is due mainly to para-articular ossicles, subluxation of the metacarpal base or synovial and fibrous tissue proliferation. Thenar atrophy and subluxation of the metacarpal proximally and radially result in a squared appearance of the hand. Atrophy of the thenar muscles (Figure 2) probably occurs because of subluxation and from disuse due to pain caused by opposition and abduction, but other mechanisms such as neural atrophy could be involved. Typically a patient with this condition will grasp by opposing the thumb tip to the distal interphalangeal joint rather than to the tip of the index finger because the latter maneuver causes greater abduction with pressure over the medial articulating surface, and hence more pain in the affected joint (Figure 6).

The disease, unless of traumatic origin, is typically bilateral. In our experience with 60 cases the incidence is about ten times greater in women than in men and the women are postmenopausal. As a rule there is no history of undue occupational trauma or fracture. Frequently members of the patient's family have Heberden's and/or Bouchard's nodes but our data are not sufficient to determine whether osteoarthritis of the carpometacarpal joints like Heberden's nodes⁵ is inherited.

In general there is no clinical evidence of widespread or generalized osteoarthritis involving large joints or the spine. Some patients with first carpometacarpal arthritis have a disease called erosive osteoarthritis which in its acute inflammatory stages may be confused with rheumatoid arthritis.⁴



Figure 2.—Thenar atrophy in osteoarthritis of the first carpometacarpal joints. The hands appear "squared" when viewed from dorsal aspect.

Occasionally in erosive osteoarthritis the first carpometacarpal joint may be eroded (Figure 3) but this contrasts with typical rheumatoid arthritis which, when it affects the wrists, is diffuse, does



Figure 3.—Erosions of the greater multangular (trapezium) and metacarpal in erosive osteoarthritis.



Figure 4.—PA film showing advanced osteoarthritis of the carpometacarpal joint with periarticular ossicles.

not involve the first carpometacarpal joint exclusively and is accompanied by generalized synovial thickening. Typically these patients do not have intermittent episodes of severe pain and inflammation in the carpometacarpal joint such as sometimes occur in the developing Heberden's or Bouchard's nodes of erosive osteoarthritis. Rather, the problem evolves insidiously, with increasing pain on grasping and wringing movements. The resultant disability ultimately impairs many fine movements that require opposition of the thumb and fingers.

Laboratory and Roentgenographic Features

Laboratory studies in patients with osteoarthritis or erosive osteoarthritis of the first carpometacarpal joints are uniformly unrevealing. Tests for rheumatoid factors are negative, and the erythrocyte sedimentation rate and thyroid function are normal.

Standard posteroanterior and oblique roentgenograms of these joints are adequate for diagnosis when the disease is advanced (Figure 4), but a special view may be very helpful in early disease.² In our modified technique the patient's forearm lies flat and fully rotated internally, with the dorsal surface of the carpometacarpal joint against the film (Figure 5). The target-to-film distance is 30 inches with the central ray directed 10 degrees cephalad from the vertical. Views of the normal joint taken in this manner are shown in Figure 6. The appearance with the thumb adducted should



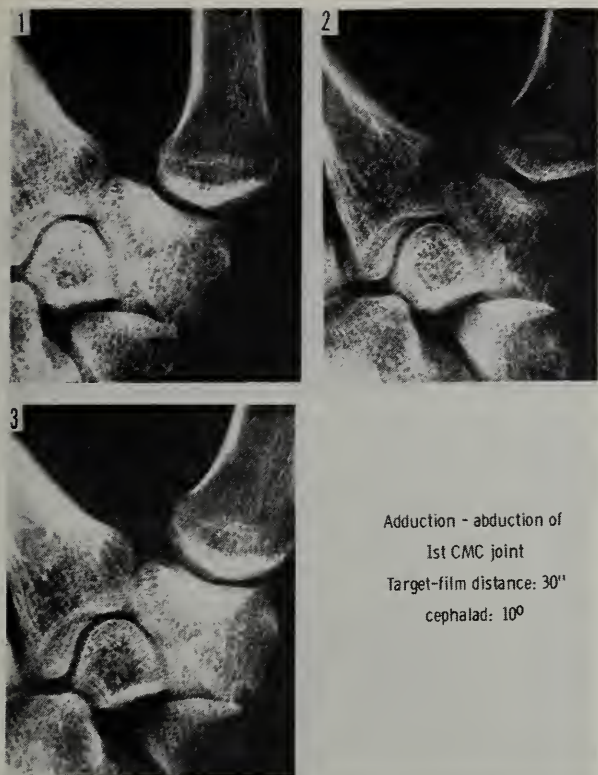
Figure 5.—Position for special view of the first carpometacarpal joint.

not be confused with lateral dislocation of the metacarpal.

Roentgenographic features of first carpometacarpal osteoarthritis include joint space narrowing, subchondral sclerosis, osteophyte formation (most frequently on the lateral trapezium), periarticular ossicles, radial subluxation of the metacarpal, and occasionally juxta-articular erosions and cysts. In these patients osteoarthritis may occasionally involve other adjacent joints of the wrists (Figure 7).

Therapy

Patients with advanced, symptomatic osteoarthritis of the first carpometacarpal joints are often not greatly benefited by acetylsalicylic acid or indomethacin. On the other hand, most patients with milder, less symptomatic disease can often be satisfactorily relieved by these drugs and dextro propoxyphene hydrochloride (Darvon).® Rest by immobilization with a leather gauntlet is of greatest benefit to severely afflicted patients who do not wish to have surgical treatment. Occasionally rest of this kind results in pronounced and prolonged



Adduction - abduction of
1st CMC joint
Target-film distance: 30"
cephalad: 10°

Figure 6.—Special view (Figure 5) showing carpometacarpal joint with thumb abducted (view 3) and adducted (view 1).

relief of pain even after the gauntlet is no longer used.

Injection of the joint with corticosteroids and local anesthetic typically produces excellent but usually transient benefit. The simple technique for injecting this joint is illustrated in Figure 8. The joint space is readily localized just proximal to the bulge caused by the base of the first metacarpal. The needle is pointed toward the base of the fourth metacarpal and inserted just ulnar to the extensor pollicis brevis tendon (the lateral border of the anatomical snuff box). When there is significant joint space narrowing and osteophytosis, the thumb may be flexed and pulled away from the trapezium to facilitate insertion of a small bore needle.

Over the past four years 12 operations were performed on eight patients (bilateral in four cases). Fewer than 7 percent of patients seen with this problem were operated on. Excision of the trapezium gave excellent or good relief of pain and improved functions of the thumb in five of seven procedures, with one patient complaining of pain and one of loss of strength postoperatively. Arthrodesis resulted in solid fusion (Figure 9) within six weeks in all five patients and they had



Figure 7.—Osteoarthritis of trapezio-navicular and trapezio-trapezoid (scaphoid) joints.

no pain and good function (Figure 10) and strength. None of the patients complained of loss of function of the thumb after arthrodesis, but this could in part reflect the severity of the arthritis preoperatively and the fact that they had compensated for loss of function even before the operation. The major indication for operation is pain intractable to the conservative measures mentioned above. Our view, which corresponds to that recently reported by Weinman and Lipscomb,⁶ is that excision of the trapezium is the operation of choice in patients with concomitant degenerative changes in the trapezio-scaphoid joint (Figure 7), lest pain in this joint remain a problem even after fusion of the trapezio-metacarpal joint. However, arthrodesis of the trapezio-metacarpal joint is indicated in patients without arthritis of the trapezio-scaphoid joint in whom a strong grip is required in their occupation. In the absence of these specific indications for excision or arthrodesis, one can employ excision of the trapezium when

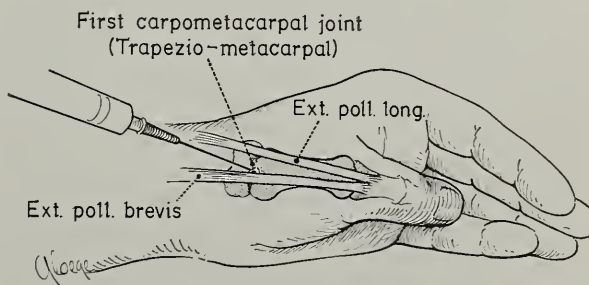


Figure 8.—Technique for injection of first carpometacarpal joint.



Figure 9.—Fused joint in wrist.

maximum mobility is desired and when some loss of strength is acceptable.

Discussion

Except for an occasional report, little has been written about osteoarthritis of the first carpometacarpal joint.^{1,3,6-7} The resultant lack of awareness allows confusion with tenosynovitis which mani-

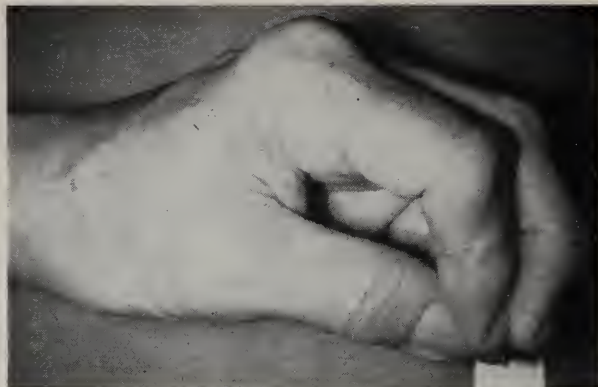


Figure 10.—Opposition after arthrodesis of first carpometacarpal joint (patient of Figure 9).

fest itself proximal (extensor-abductor tenosynovitis of de Quervain) or distal (flexor tenosynovitis) to the carpometacarpal joint. Even when the disease is recognized, a nihilistic attitude toward osteoarthritis too frequently results in advice that "nothing can be done" for this disabling arthritis of the hand. Our experience shows that both medical and surgical measures can greatly benefit the severely symptomatic patient.

REFERENCES

1. Aune, S.: Osteoarthritis in the first carpometacarpal joint, *Acta Chir. Scand.*, 109:449-456, 29 Oct. 1955.
2. Lasserre, C., Pauzat, D. and Derrennes, R.: Osteoarthritis of the trapeziometacarpal joint, *J. Bone Joint Surg. (British)*, 31-B:534-536, Nov. 1949.
3. Murley, A. H. G.: Excision of the trapezium in osteoarthritis of the first carpometacarpal joint, *J. Bone Joint Surg. (British)*, 42-B:502-507, Aug. 1960.
4. Peter, J. B., Marmor, L. and Pearson, C. M.: Erosive osteoarthritis of the hands, *Arthritis Rheum.*, 9:365-388, June 1966.
5. Stecher, R. M.: Heberden's Nodes. A clinical description of osteoarthritis of the finger joints, *Ann. Rheum. Dis.*, 14:1-10, March 1955.
6. Weinman, D. T., and Lipscomb, P. R.: Degenerative arthritis of the trapeziometacarpal joint: arthrodesis or excision, *May Clinic Proceedings*, 42:276-287, May 1967.
7. Ylzarbe, E.: Osteoarthritis of the first metacarpal, *Rheumatism*, 22:68-70, July 1966.

Detection of Narcotic Use

Comparison of the Nalorphine (Pupil) Test With Chemical Tests

H. W. ELLIOTT, M.D., PH.D., *Orange*; N. NOMOF, M.D., K. D. PARKER,
M. CRIM.,* G. R. TURGEON, M.D., *San Francisco*

■ *The nalorphine (pupil) test for narcotic abuse is widely used in California. It is based on the ability of nalorphine to produce mydriasis in subjects who have recently taken morphine-like drugs and to produce miosis in others. The test will usually detect as little as 15 mg of morphine or comparable doses of other narcotics for several hours except in special circumstances. It is even more reliable for detection of chronic use of narcotics. A simple card pupillometer is adequate for measuring changes in pupil size resulting from nalorphine.*

Analysis for narcotics in urine by thin layer chromatography is also used, either alone or in conjunction with the pupil test, to detect drug abuse. In one study which included many urine specimens from subjects who had negative pupil tests the correlation between the pupil test and urinalysis was good (85 percent). When urinalysis was used to confirm suspicion of drug use resulting from a positive or equivocal pupil test, inter-method agreement dropped to about 50 percent for various reasons. Even so, use of the pupil test for screening and urinalysis for confirmation provides a satisfactory program for detection of narcotic abuse.

ATTEMPTS TO CONTROL the illicit use of narcotics in California, which has an estimated 18,000 heroin users, have included the application of the

*Master of Criminology.

From the Hine Laboratories; the Department of Pharmacology and Experimental Therapeutics, University of California Medical Center, San Francisco, and the Narcotic Control Division, Department of Corrections, Parole and Community Services Division, State of California.

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Reprint requests to: Department of Medical Pharmacology and Therapeutics, University of California, Irvine, California College of Medicine, Orange County Medical Center, 101 South Manchester Avenue, Orange 92668 (Dr. Elliott).

nalorphine pupil test introduced by Terry and Braumoeller in 1955⁸ and, more recently, analysis of urine for narcotics or their metabolites.^{1,5} Usually, willingness to undergo the tests at any time is made a condition of parole; they are used at the discretion of the parole officer. Subjects come to testing centers in the metropolitan areas at specified times, or are brought in for testing by surprise. The program is extensive; in 1964 about 3,000 parolees took the nalorphine test an average of three times a month; and a few months after

urinalysis was started in May 1964, 1,200 specimens a month were being examined for the presence of narcotics. This figure rose to 2,000 a month by December 1965.

The pupil test is based on an apparent antagonism between nalorphine (or levallorphan) and the morphine-like drugs. If a person has a sufficient amount of narcotic (codeine excepted) in his body (presumably enough to cause subjective effects and such objective effects as miosis), as little as 3 mg of nalorphine will usually produce mydriasis or the pupil diameter will not change. If there is little or no narcotic in the body, the usual effect of nalorphine is miosis. Consequently, the subject who exhibits mydriasis after nalorphine is suspected of using a narcotic; miosis suggests that he is not using a narcotic, at least has not used it in the period immediately preceding the test. The test is described in a pamphlet issued by the State of California Department of Public Health.⁷

Detection of narcotics in the urine has become a practical method of determining narcotic use since the development of relatively simple and inexpensive analytical procedures capable of detecting 1 to 5 mcg per ml of narcotic in the urine. Two tests have been developed,⁵ one (Test A) for morphine and derivatives (heroin is metabolized to morphine), and the other (Test B) for synthetic narcotics and amphetamines. They are based on extraction of drugs from urine, and separation and identification by thin layer chromatography. The methods are fully described in a manual issued by the United States Public Health Service.⁶

At present, in California, parolees are brought to testing centers, the nalorphine test is carried out, and if results are positive or equivocal (no change in pupil size), or if there is any reason for suspicion (such as needle marks) a urine specimen is collected and sent to the laboratory for analysis. Urinalysis is not yet so simple and inexpensive that all parolees can be checked by this method; hence it is desirable to know the advantages and disadvantages of the pupil and urine tests so they can be utilized most efficiently.

The nalorphine test was widely applied in the field⁸ before it was examined under controlled conditions. However, when its use was extended to the entire state, its general usefulness and reliability were determined by measuring the effects of nalorphine and levallorphan on the pupil diameter of untreated subjects² and subjects given

known doses of narcotics,³ and by comparing the results of pupil tests done in the field with results of analysis, for morphine and metabolites,⁹ of urine specimens taken simultaneously with the pupil test. The pupil test has also been evaluated in Orientals heavily addicted to heroin and opium¹⁰ and in subjects given single and multiple doses of codeine.⁴ It is surprisingly safe. No reports of serious side effects have appeared even though more than 100,000 tests are being administered yearly in California.

The magnitude of pupil diameter changes to be expected following administration of known doses of narcotics or of nalorphine has been determined by a photographic method on volunteer subjects at the California State Medical Facility, and enough data are now available to predict results with fair accuracy. In our studies, the test consists of determining pupil diameter in a constantly lighted testing area, administering 3 mg of nalorphine intramuscularly, and measuring pupil diameter again 30 minutes later. Possibly reading at 20, 30 and 40 minutes would be more accurate,¹⁰ but since in the field there is generally time for only one reading, we have used the 30-minute interval to conform to established practice.

Miosis produced by 3 mg of nalorphine amounted to -0.3 mm or more in a previous study.² Subsequently, in 200 subjects given nalorphine after a placebo, the average decrease in pupil diameter was 0.76 mm. In ten subjects false positive readings ($+0.1$ mm or greater) were obtained, so that the apparent accuracy was 95 percent. However, the true accuracy was probably 99 percent since eight of the ten subjects who gave false positive tests also received eye drops containing a mydriatic or miotic agent which could have influenced the test. At one testing center the incidence of positive nalorphine tests ($+0.25$ mm or greater) was 0.39 percent in more than 60,000 tests and 0.2 percent in more than 50,000 tests the following year. Since some of these were true positives, the incidence of false positives was therefore even lower. The decrease in pupil size is enough to be easily determined with a simple card pupillometer, but since pupil size may vary spontaneously between two readings, a few false positive tests are probably unavoidable. The proportion of false positives could undoubtedly be reduced by making several readings or by increasing the dose of nalorphine, but the latter would increase the incidence of unpleasant side effects.

TABLE 1.—Correlation of the nalorphine pupil test results using three methods simultaneously applied to measure the pupil diameter changes in subjects who received the drug or placebo in selected experiments conducted during 1962 to 1964.

Date	Drug and dose mg I.M.	Hour of challenge	3 mg nalorphine	No. of subjects receiving		No. of subjects receiving drug with pupil change									No. of subjects receiving placebo and corresponding pupil change					
						Hole			Card			Camera			Hole		Card		Camera	
				Drug	Placebo (f)	+	±	—	+	±	—	+	±	—	+	±	—	+	±	—
10/ 7/62	Morphine 15	2	11	1	5	6	0		3	4	4	8	3	0	0	0	1	0	0	1
10/21/62	Morphine 30	2	11	1	3	1	7		7	3	1	7	3	1	0	0	1	0	0	1
11/17/62	Morphine 45 ^(a)	3	10	4	3	6	1		8	1	1	8	2	0	0	0	4	0	0	4
2/ 9/63	Methadone 15	2	13	2	6	4	3		7	5	1	11	2	0	0	1	1	0	0	2
10/19/63	Heroin 5	2	13	1	5	7	1		5	7	1	11	1	1	0	1	0	0	1	0
5/ 2/64	Methadone 15 ^(b)	3	12	3	8	2	2		8	1	3	10	0	2	0	0	3	0	0	3
3/21/64	Methadone 15	6	13	2	10	1	2		9	1	3	9	3	1	0	0	2	0	0	2
4/18/64	Methadone 15 ^(c)	2	12	3	9	2	1		10	0	2	10	1	1	0	0	3	0	0	3
6/17/64	Methadone 15 ^(d)	3.5	10	5	8	2	0		9	0	1	9	0	1	0	1	4	0	0	5
6/17/64	Heroin 10	2	11	3	6	2	3		10	0	1	8	0	3	0	0	3	0	0	3
9/12/64	Methadone 15 ^(e)	2	10	5	5	5	0		7	1	2	9	0	1	0	0	5	0	0	5
11/12/64	Methadone 15	3	10	5	4	3	3		6	2	2	9	0	1	0	0	5	0	0	5
Totals				136	35	72	41	23	89	25	22	109	15	12	0	3	32	0	1	34
Percentages				100	100	53	30	17	65	18	16	80	11	9	0	9	91	0	3	97
						83			83			91								

(a) Received morphine 3 x 15 mg I.M. in 5 hours and were challenged 3 hours after the last dose.

(b) Also received amphetamine 40 mg I.M. at hour 2.

(c) Also received amphetamine 20 mg I.M. at hour 1.

(d) Also received amphetamine 40 mg I.M. at hour 1.5.

(e) Also received scopolamine 1 mg I.M. at hour 1.

(f) Placebo was pentobarbital 90 mg I.M.

+

 Increase in pupil diameter; positive nalorphine test.

±

 No change in pupil diameter; equivocal test.

—

 Decrease in pupil diameter; negative test.

Simultaneous tests made with the card, with a hole pupillometer,² and with a camera have established that the camera is only slightly superior to the simple pupillometers except for the fact that the photographic method provides a permanent record. As shown in Table 1, in 12 experiments involving 136 subjects given narcotics, 91 percent of the tests conducted with the camera were positive or equivocal, while the comparable figure for the card and hole pupillometer was 83 percent. In 35 subjects given placebos, all three methods yielded negative tests in more than 90 percent of the cases. The results indicate that the simple pupillometers are adequate for field work and should not produce many false positive tests, since the average decrease in pupil diameter due to nalorphine after placebo is 0.76 mm.

Since narcotic use can be either continuous or in sprees, the nalorphine test has been administered after single doses of various narcotics, and during and after continuous administration of morphine and codeine. The test results are usually positive for two to four hours after single intramuscular doses of morphine (15 mg), heroin (5 mg), methadone (15 mg), meperidine (Demerol®) (150 mg), and oxycodone (narcotic in Percodan®) (25 mg), but not after codeine (90

mg), d-propoxyphene (Darvon®) (200 mg) or dextromethorphan (Romilar®) (90 mg). When the tests were given at intervals up to 36 hours after 15 mg of morphine, results of about half were negative at six hours, and 90 percent were negative at 12 hours. After single doses of narcotics, 3 mg of nalorphine increases the pupil diameter about 0.2 mm. Efforts to raise this value by increasing the dose of nalorphine or by giving three 15-mg doses of morphine every two hours were unsuccessful.³

When 15 mg doses of morphine were given every six hours for five days to 30 subjects, response to the nalorphine test four hours after the seventh dose of morphine was negative in only one subject; and results were positive in nine subjects 20 hours after the last dose.³ The increase in pupil diameter averaged 0.4 mm. Thus, not surprisingly, the test is a more reliable indicator of chronic than of sporadic morphine use. This conclusion was substantiated by a study of heroin and opium addicts,¹⁰ in which it was noted, however, that either giving a large dose of heroin intravenously shortly before the test, or the onset of severe withdrawal symptoms, could prevent pupillary dilation after nalorphine administration.

A negative response to the nalorphine test after

a dose of propoxyphene (the response was positive in three of fifteen subjects) or dextromethorphan was expected, since these drugs have only minimal morphine-like actions. Codeine has been studied more thoroughly in this regard, because it can reverse a potentially positive reaction if given with nalorphine,⁴ and because subjects taking codeine regularly respond positively after a few days.³ In a study in which the oral dose of codeine was increased over a period of five days from 60 to 240 mg every six hours, most subjects responded positively on the third day. The degree of positivity correlated roughly with urinary concentrations of morphine, which is a minor metabolite of codeine. However, four subjects given a continuous intravenous infusion of 30 mg codeine per hour reacted positively to the nalorphine test during the ninth hour of infusion, suggesting that development of tolerance to codeine is responsible for development of a positive response to the nalorphine test.⁴

Possible antagonists to the agents used for the pupil test have been considered, since miotic or mydriatic drugs could interfere with their action. The miotic drugs pilocarpine and chlorpromazine make the test more difficult by forcing the observer to measure small pupils, but do not qualitatively alter the usual pupillary effects of narcotics and antagonists; nor do single doses of the mydriatics atropine, scopolamine, homatropine, amphetamine or methamphetamine have such an effect. The actions of locally administered sympathomimetics are complex and need further study. The best antagonists are the narcotics themselves. Morphine or heroin given in conjunction with nalorphine overwhelms the usual 3 mg dose of nalorphine and produces a false negative response to the test. Codeine also has such an effect, but the mechanism of its action is not clear, since negative results occur with codeine-to-nalorphine ratios between 5:1 and 60:1.

Under controlled conditions, sporadic narcotic use can be detected more reliably by urine analysis than by the pupil test. Thus, 36 hours after one 15 mg dose of morphine, 85 percent of urine specimens from 30 subjects were positive for morphine; whereas the pupil test had positive results in only one subject.³ Furthermore, occasional use of codeine is not detected by the pupil test, but metabolites of a single dose should appear in the urine for 24 to 48 hours. In a large program such as that in California, if there is a high degree

of correlation between the pupil and urine tests, it would be more economical to reserve urinalysis for suspected cases. When the question of such a correlation was first studied by analytical methods that would not detect synthetic narcotics, there was agreement in 85 percent of 419 comparisons.⁹ This satisfactory correlation was partially the result of the relatively large number (373) of negative responses to the pupil tests reported, since experimental work indicates that few false positive responses to this test should occur.

Since the incorporation of urinalysis into the testing program there has been an opportunity to compare the pupil and chemical tests under the special condition that urinalysis was requested when the response to the pupil test suggested drug use. Thus, during the last seven months of 1964, at one testing center about 40,000 pupil tests were performed on approximately 1,200 subjects and 1,004 urine specimens were submitted for analysis. Forty-seven percent of 160 subjects with positive response to the pupil test, and 20 percent of 844 subjects with equivocal response had evidence of drug usage in the urine (Test A).⁵

It should be noted that half the subjects who reacted positively to the pupil test, and whose urine did not contain the drug, either admitted use of heroin within the previous 48 hours or had fresh needle marks.

Statistics compiled by the same testing center for the period of August 1965 to July 1966 are similar to those of 1964 even though urinalysis was performed by a different laboratory and Test B was made when requested. About 50,800 pupil tests yielded 101 positive and 1,019 equivocal readings. Urine specimens were analyzed from 1,075 of these 1,120 subjects, with the results shown in Table 2. Morphine (or heroin) was

TABLE 2.—Comparison of the pupil and chemical tests in a group of subjects whose response to the pupil test was positive or equivocal.

	URINALYSIS		PUPIL TEST			
	<i>Subjects N = 1,075</i>		88 Positive		987 No Change	
			POSITIVE		NO CHANGE	
	Percent	Number	Percent	Number	Percent	Number
Test A positive	52.3	46	13.6	134		
Test B positive	1.1	1	1.1	11		
Morphine	47.7	42	10.8	106		
Codeine	1.1	1	1.3	13		
Oxycodone			0.1	1		
Morphine + Codeine	3.4	3	1.3	13		
Morphine + Oxycodone			0.1	1		
Meperidine			0.3	3		
Methadone			0.3	3		
Methamphetamine	1.1	1	0.5	5		

found in the majority of cases and codeine in a few. Use of Test B did not materially improve the correlation between the results of the pupil and chemical tests, although both meperidine and methadone were detected.

The correlation between responses to pupil and chemical tests seems low when compared with our original study,⁹ but this is largely the result of differences in sample. In the 1964 and 1965 series, urine specimens were collected only from the select group of subjects whose pupillary reaction to nalorphine was suggestive of narcotic use, whereas urine specimens used in the original study included those from the much larger group of negative reactors as well. Even so, a roughly 50 percent incidence of positive response to the pupil test in subjects whose urine contained no drug is disturbing and suggests that neither the pupil nor the chemical tests may be as reliable in the field as under controlled conditions.

There are several possible reasons for the discrepancy aside from such obvious ones as errors in reading pupil size and in obtaining urine specimens or in the chemical procedures themselves. The most important are that emotion or various stimuli may alter pupil size, and that perhaps 1 percent of the population will not consistently

show measurable miosis after 3 to 4 mg of nalorphine.

We conclude that a program for detection of narcotic abuse should include the pupil test for screening, and that the urine should be analyzed when the response to the pupil test suggests a narcotic is being used.

REFERENCES

1. Davidow, B., Petri, N. L., Quame, B., Searle, B., Fastlich, E. and Savitzky, J.: A thin-layer chromatographic screening test for the detection of users of morphine or heroin, *Am. J. Clin. Path.*, 46: 58-62, July 1966.
2. Elliott, H. W. and Way, E. L.: Effect of narcotic antagonists on the pupil diameter of nonaddicts, *Clin. Pharmacol. Ther.*, 2:713-721, Nov.-Dec. 1961.
3. Elliott, H. W., Nomof, N., Parker, K., Dewey, M. L., and Way, E. L.: Comparison of the nalorphine test and urinary analysis in the detection of narcotic use, *Clin. Pharmacol. Ther.*, 5:405-413, July-Aug. 1964.
4. Elliott, H. W., Nomof, N., and Parker, K. D.: Correlation of the nalorphine test with concentration of metabolites in the urine after single doses and continuous administration of codeine, *Clin. Pharmacol. Ther.*, 8:78-85, Jan.-Feb. 1967.
5. Parker, K. D., Hine, C. H., Nomof, N. and Elliott, H. W.: Urine screening techniques employed in the detection of users of narcotics and their correlation with the nalorphine test, *J. Forensic Sci.*, 11:152-166, April 1966.
6. Parker, K. D. and Hine, C. H.: Manual for the determination of narcotics and dangerous drugs in the urine, *Psychopharm. Bull.*, 3:18-42, July 1966.
7. State of California Department of Public Health, Berkeley, California, Recommended procedure for narcotic use testing of probationers and parolees, 1961.
8. Terry, J. G. and Braumoeller, F. L.: Nalline: An aid in detecting narcotic users, *Calif. Med.*, 85:299-301, Nov. 1956.
9. Way, E. L., Elliott, H. W. and Nomof, N.: Comparison of the chemical tests with the pupillary method for the diagnosis of narcotic use, *Bull. on Narcotics*, 15:29-33, Jan.-March 1963.
10. Way, E. L., Mo, B. P. N., and Quock, C. P.: Evaluation of the nalorphine pupil diagnostic test for narcotic usage in long-term heroin and opium addicts, *Clin. Pharmacol. Ther.*, 7:300-311, May-June 1966.

HALTING HICCUPS IN ANESTHETIZED PATIENTS

"A minor, but very useful, new treatment: the halting of hiccups in the unconscious or anesthetized patient by stimulation of the pharynx opposite the second cervical vertebra by means of a catheter passed through the nose. An abrupt back-and-forth movement of the catheter immediately interrupts hiccups—apparently by interrupting vagal impulses. If hiccups recurs, the same maneuver is equally effective in stopping it."

—SHELDON S. WALDSTEIN, M.D., Chicago
Audio-Digest *Anesthesiology*, Vol. 10, No. 11

Sodium Content of Community Water Supplies in California

RUTH C. STEINKAMP, M.D., CLARENCE L. YOUNG, B.S.,
DOLORES NYHUS, M.S., AND ARNOLD E. GREENBERG, S.M., *Berkeley*

■ *The amount of sodium ion in water used for ingestion may be critical in effective use of a low sodium dietary regimen. Waters containing not over 20 mg of sodium per liter are provided for in the sodium restricted diets set forth by the American Heart Association. For diets containing more than 500 mg of sodium a day, waters of greater sodium content may be used if proper dietary adjustments are made.*

While assessment of the long-term average sodium content of a community water supply is difficult, the determined values for sodium lend to classification within range categories. The larger community water supplies in California are presented within several range categories of sodium content.

The more commonly used water softeners add sodium to water. The sodium-restricted patient should be cautioned against their use. Similar consideration should probably be given to water supplies of retirement communities where the potential for disorders requiring sodium restriction is greater than in the general population.

THE EFFECTIVE USE of sodium restricted diets in the treatment of conditions such as congestive heart failure, hypertension, liver disease or other disease depends upon a critical value of sodium ion in water for ingestion as well as adherence to a diet low in this element. Failure to recognize this may contribute to or result in non-response to sodium restriction.⁴

For several years, the California State Department of Public Health has sampled community

water supplies within the state for sodium analysis. These data may not be readily available to the practicing physician. The purpose of this paper is to present this information and to consider briefly some related factors.

Sodium in Water Related to Total Sodium Intake

The sodium restricted diets promulgated by the American Heart Association are probably the most widely accepted materials of their kind.^{7,8} For the 500-milligram sodium restricted diet, the quantity and variety of foods allowed provide approximately 440 mg of sodium a day. The addi-

From the Bureau of Public Health Nutrition, Bureau of Sanitary Engineering, and the Sanitation and Radiation Laboratory, California State Department of Public Health, Berkeley.

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Reprint requests to: Bureau of Public Health Nutrition, State Department of Public Health, 2151 Berkeley Way, Berkeley 94704 (Dr. Steinkamp).

tional 60 mg may derive from water. The average adult intake of water should be about 2.2 liters a day. In order not to exceed the prescribed total of 500 milligrams, water containing not over 20 mg of sodium per liter is indicated for drinking and for cooking.

The 1,000 milligram sodium restricted diet is based on the 500-milligram sodium restricted diet and the use of water with a similarly low sodium content. The additional 500 mg of sodium may be acquired by the addition of one-fourth teaspoon of salt (equivalent to about 500 mg sodium) or by using designated quantities of selected foods which individually or collectively contain 500 mg of sodium. Should the sodium content of water for ingestion be greater than 20 mg per liter, the potential sodium intake from water should be calculated and appropriate adjustments in the diet made. Use of water containing over 250 mg of sodium per liter would contribute more than the additional 500 mg allowed and thus is contraindicated. Because sodium content of community water supplies may fluctuate (for reasons considered below) water supplies containing over 200 mg of sodium per liter should probably also be interdicted.

The assessment of the long-term average sodium content of a community water supply is difficult. There are a number of reasons for this. Among the factors are:

1. Natural sources of sodium, such as
 - a. seasonal fluctuations associated with rainfall and runoff,
 - b. leaching from underground sodium salt deposits,
 - c. sea water intrusion in coastal areas,
 - d. ion exchange via earth deposits resulting in replacement of some other element by sodium;
2. Artificial sources of sodium, such as
 - a. use of sodium containing salts for purification or softening of water,
 - b. use of brine regenerated zeolite exchange resins in either community or home water softener systems; and
3. Capacity and manipulation for distribution of water in the community, as for example:
 - a. the existence of more than one purveyor using more than one water source for the total community, and
 - b. the use, by a single purveyor to the community, of water sources having differing

sodium contents with the delivery of varying blends of water at different times.

These and other considerations outside the scope of this paper have been presented previously.^{3,9}

Of particular importance, especially in hard water areas such as most of Southern California, is the frequent use of softeners for removal of dissolved calcium and magnesium. This may be done either at the community or the home level. The usual softening process (brine regenerated zeolite) substitutes sodium for the elements that cause hardness. For every 100 mg of hardness removed, 50 mg of sodium are added per liter of water. This amount of sodium is additive to the amount present in unsoftened water.

The less common acid regeneration type of softener does not add sodium to the treated water. This type may be recommended for use by persons on a low sodium regimen or for retirement communities where the potential for disorders requiring sodium restriction is greater than in the general population.

Sodium in California Community Water Supplies

The data reproduced by sodium category in the accompanying tables were determined by either the Sanitation and Radiation Laboratory of the California State Department of Public Health or by the Branch Public Health Laboratory (Los Angeles) by flame photometry.^{1,6} In most instances, more than one sample was analyzed for a single community water supply. In all cases, the largest sodium value obtained during the most recent year of sampling since 1951 was used for listing the community within the several sodium content categories (see appendix). The categories were arbitrarily selected so as to conform to the American Heart Association standards. Communities having more than one water purveyor and comparable sodium values are simply listed in the appropriate category. Communities having more than one water purveyor, the supplies of which differed in sodium content, are listed in the appropriate several sodium categories with notation of purveyor identity. Information about water supplies for unlisted communities may be obtained from the water purveyor or the local health department. A recent nationwide survey of sodium ion in water supplies² included 21 communities in

California. Values listed in that survey are comparable to those reported here.

Implications for Physician and Patient

When it is essential that a patient restrict his sodium intake, cognizance must be taken of the sodium content of ingested water. The most rigid approach is for the patient to use distilled or de-ionized bottled water for drinking and cooking. This approach may be necessary in communities having high sodium content in the water supply. Care must be taken to avoid waters which are labeled "spring pure," "spring fresh" or by other similar designation. These labels do not indicate the sodium content. Spring waters should not be used unless the sodium level has been established as being satisfactorily low by analysis.

Use of the community water supply imposes less restriction for the patient and may be allowed in many areas of California. With the data presented here, supplemented by information from the water purveyor, it may be possible to establish that the community water is indeed acceptable for sodium restricted diets. Because of the many uncertainties involved, it may not be as desirable for

rigid sodium control as the use of distilled or de-ionized water.

Farag and Mozar⁵ recently demonstrated that subsequent admission to hospital of patients with congestive heart failure was considerably reduced by intensive follow-up services provided by the nutritionist, nurse and health educator. The data presented here should be of value to these disciplines as well as to the physician in counseling patients who need sodium restriction.

REFERENCES

1. California Domestic Water Supplies, State of California, Department of Public Health, 1962.
2. Cooper, G. R.: Personal communication.
3. Cooper, G. R., and Heath, Beth: Sodium ion in drinking water.
2. Importance, problems, and potential applications of sodium-ion-restricted therapy, *J. Am. Diet. Assoc.*, 50:37, 1967.
4. Elliott, G. B., and Alexander, E. A.: Sodium from drinking water as an unsuspected cause of cardiac decompensation, *Circulation*, 23:562, 1961.
5. Farag, S. A., and Mozar, H. N.: Preventing recurrent heart failure, *J. Am. Diet. Assoc.*, 51:26, 1967.
6. Sodium Values of Drinking Water, California Heart Association and State of California, Department of Public Health, Feb. 1960.
7. The Sodium Restricted Diet: 500 milligrams, Published by Am. Heart Assoc., Sept. 1965.
8. The Sodium Restricted Diet: 1,000 milligrams, Published by Am. Heart Assoc., Nov. 1966.
9. White, J. M., Wingo, J. G., Alligood, L. M., Cooper, G. R., Gutridge, J., Hydaker, W., Benack, R. T., Dening, J. W., and Taylor, F. B.: Sodium ion in drinking water. 1. Properties, Analysis and Occurrence, *J. Am. Diet. Assoc.*, 50:32, 1967.

See Appendix California Community
Water Supplies by Sodium Content Category



APPENDIX

California Community Water Supplies by Sodium Content Category

NOTE: Many towns and communities in the list below are served by more than one supplier of water. Hence the sodium content may vary from one part of the community to another. In such cases the name of the town or community may be listed under several of the classifications of sodium concentration. It is important, in such split communities, to determine precisely where a patient lives and what water supplier is serving him.

≤20 mg/L	21-50 mg/L	51-100 mg/L	101-200 mg/L	*201-250 mg/L ** >250 mg/L
Alameda	Alamo	Alvarado	Adelanto	
Albany	Alhambra	Antioch	Agoura	
Al Tahoe	Alisal	Anza Village	Altadena	
Anderson	Alturas	Armona	Anaheim	
Arden Manor	Alviso	Artesia	Apple Valley	
Arden Park	Aptos	Atascadero	Arvin	
Auburn	Arbuckle	Athens (L. A. Co. Water Works Dist. #1)	Avalon	
Azusa	Arcadia		Avenal	
	Arcata		Avila*	
	Arroyo Grande			
	Athens (Athens Water Co.)			
	Atherton			
	Atwater			
Baldwin Park (Baldwin Park Co. Water District, Park Water Co. #26, Valley View Mutual Water Co., Warner Acres Tract Mutual Water Co.)	Bakersfield Vicinity (Calimar Water Co., Vaughn Mutual Water Co.)	Bakersfield (Garden Water Corp.)	Bakersfield (California Water Service Co.)	
Bass Lake	Banning	Baldwin Hills	Bakersfield Vicinity (East Niles Community Service)	
Bear Valley	Bassett-Baldwin Park (San Gabriel Valley Water Co.)	Baldwin Park (San Gabriel)	Barstow**	
Bellflower (Home Garden Mutual Water Co.)	Baywood Park	Bellflower (Bellflower Mutual Water Co., Peerless Land and Water Co., Somerset Mutual Water Co.)	Bell Gardens (So. Calif. Water Co.)	
Belmont	Beaumont	Bishop	Benicia	
Belvedere	Bellflower (Berlu Water Co.)	Borrego Springs	Beverly Hills	
Ben Lomond	Bell Gardens (Coast Water Co., Park Water System #3)	Brea	Blythe	
Berkeley	Big Bear Lake	Brentwood	Boron**	
Big Bear	Buena Park (City)	Buellton	Brawley	
Big Bear City		Buena Park (Homewood Mutual Water Co.)	Burbank	
Biggs				
Big Pine				
Black Point				
Bloomington				
Boulder Creek				
Broadmoor				
Brockway				
Brookdale				
Buckeye				
Burlingame				
Camp Meeker	Calwa	Calimesa	Calabasas	
Camp Nelson	Cambria	Cambria Pines	Callexico	
Carmel	Campbell	Capitola	California City	
Carmel Highlands	Carmel Valley	Caruthers	Calapatria	
Carmichael Vicinity (Arden Park Vista Water Maintenance Dist.)	Carmichael (Carmichael Irrigation Dist.)	Castroville	Camarillo	
Carnelian Bay-Cedar Flat-Panorama Estates	Carmichael Vicinity (Northridge Park Co. Water Dist.)	Centerville	Carlsbad	
Casaloma	Cathedral City	Ceres	Carpinteria	
Cedar Pines Park	Cayucos	Chino (City)	Clayton	
Chico	Chowchilla	Citrus Heights (Citrus Heights Irrigation Dist.)	Coalinga*	
Chino (Park Water Co., So. Cal. Water Co.)	Citrus Heights Vicinity (Lincoln Oaks Water Co.)	Colusa	Commerce	
Citrus Heights Vicinity (Royal Oaks Water Co.)	Claremont	Corcoran	Compton (City, Park Water Co.)	
Clearlake Highlands	Clovis	Corralitos	Concord	
Clearlake Oaks	Coachella	Costa Mesa (Costa Mesa Co. Water Dist.)	Contra Costa County Water District	
Clearlake Park	Compton (Richland Farms Mutual Water Co., So. Cal. Water Co., Uehling Water Co.)	Cudahy	Costa Mesa Area (Santa Ana Heights Water Co.)	
Cloverdale	Compton Vicinity (Central Gardens Water Co.)	Cupertino	Crockett	
Colfax	Cotati		Cucamonga	
Colton	Covina		Culver City	
Corning	Cuesta La Honda			
Corte Madera	Cutler			
Cottonwood	Cypress			
Crescent City				
Crestline				

APPENDIX (Continued)

California Community Water Supplies by Sodium Content Category

NOTE: Many towns and communities in the list below are served by more than one supplier of water. Hence the sodium content may vary from one part of the community to another. In such cases the name of the town or community may be listed under several of the classifications of sodium concentration. It is important, in such split communities, to determine precisely where a patient lives and what water supplier is serving him.

≤ 20 mg/L	21-50 mg/L	51-100 mg/L	101-200 mg/L	* 201-250 mg/L ** > 250 mg/L
Del Monte Fairways Del Paso Manor Donner Lake Dunsmuir Durham	Danville Delhi Denair Diablo Dinuba Duarte	Daly City Davis Decoto Dixon Dominguez Dorris Dos Palos Downey	Delano Desert Hot Springs	
East Monterey Edgemar El Cerrito El Dorado El Monte (Farm Mutual Water Co., Rurban Homes Mutual Water Co.) Emeryville Etiwanda	Earlimart East Cliff Area East Palo Alto East Pasadena Edgemont El Granada Elk Grove El Modena (Orange County Water Works) El Monte (City, Del Rio Mutual Water Co., San Gabriel Valley Water Co.) El Monte-Garvey Elsinore Vicinity (Elsinore Water Dist.) Enterprise Escalon Esparto Eureka (City) Eureka Vicinity (Humboldt Community Service Dist.) Exeter	East San Bernardino Elsinore Vicinity (Elsinore Valley Municipal Water Dist.)	East Bakersfield East Los Angeles, Belvedere El Cajon El Centro El Modeno (Santiago Water Co.) El Rio El Segundo* Elsinore (City) Encinitas Escondido	
Fairfax Fair Oaks Fall River Mills Fallsvale Farmersville Felton Ferndale Fetters Spring Fields Landing Florin Folsom Forest Hill Forestville Vicinity Fort Bragg Foster City Fruitridge Vista	Fernwood Firebaugh Florence Fowler Fresno Fresno Vicinity (Bakman Water Co.) Friendly Acres Fullerton (Lansdowne Water Co.)	Fontana Freedom Fremont	Fallbrook Fillmore Flintridge Frazier Park Fullerton (City)	
Galt Garberville Gardenland Area Gerber Gilroy Grass Valley Green Valley Gridley	Garden Grove Garden Grove Vicinity Glen Avon Heights Greenfield Guerneville	Gardena Vicinity Gardena-Lawndale Vicinity Garden Acres Glendora (Suburban Water Systems) Grover City Gustine	Gardena Glendale Glendora (City) Glen Ellen Goleta Gregory Gardens Guadalupe	
Hayfork Healdsburg Vicinity (Fitch Mountain Water Co.) Highway City	Half Moon Bay & Vicinity Hamilton City Healdsburg (City) Hercules Hesperia	Hanford Hayward Hemet Highland Park Hillsborough	Hawthorne Hawthorne Vicinity-Liberty Acres Helix Irrigation District Hermosa Beach - Redondo Beach Hidden Hills Highgrove Highland Hollister Hollister Vicinity Holtville	

APPENDIX (Continued)

California Community Water Supplies by Sodium Content Category

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≤20 mg/L	21-50 mg/L	51-100 mg/L	101-200 mg/L	*201-250 mg/L ** >250 mg/L
			Home Gardens Hope Ranch Huntington Beach** Huntington Park	
Idyllwild Idyllwild Vicinity Independence Inyo	Indio Indio Vicinity Ivanhoe	Inverness Irvington	Industry Inglewood* Isleton	
Jackson Jamestown	Joshua Tree			
Kentfield Kerman Kings Beach	Keyes Kingsburg	Kernville	Kagel Canyon* Kennelva	
Lake Arrowhead Lake Arrowhead Vicinity Lakeport Lake Tahoe, So. Shore Larkspur La Selva Beach Lincoln Linda Linda Mar Lockford Lone Pine Loomis Loyalton Lucerne	Lafayette Lakewood (Ideal Petroleum Co.) La Puente (L. P. Valley County Water Dist.) La Puente Vicinity (Suburban Water Systems) La Verne Little Rock Vicinity (Sun Valley Village Water & Improvement Co.) Livingston Lodi Los Banos Los Molinos Los Osos Lynwood Vicinity (Lynwood Gardens Mutual Water Co.)	La Habra Heights (L.H.H. Mutual Water Co.) Lakewood (City) Lamont Lancaster La Puente (Cross Water Co., Vallecito Water Co.) Lenwood Little Rock (Little Rock Creek Irrigation Dist.) Little Rock Vicinity (L.A. Co. Water Works Dist.) Loma Linda Lompoc Vicinity Los Alamitos Los Alamos Los Altos Los Angeles Vicinity (Watts) Los Angeles Vicinity (Florence-Graham) Los Gatos Lynwood (City)	La Canada La Crescenta Laguna Beach La Habra (City) Lakeside Vicinity (River-view Water District) La Mesa La Mirada La Sierra Heights-Arlington Lawndale Lemon Grove Lemoore Liberty Acres (Hawthorne) Lindsay (City)** Lindsay (Lindsay-Strathmore Irrigation Dist.) Livermore* Lomita Lompoc Long Beach* Los Angeles (City)*	
Madera Mammoth Mariposa Mentone Menlo Park (City) Meyers Mill Valley Mokelumne Hill Monte Vista Mt. Herman Park Mt. Shasta Murphys Area Muscoy (Muscoy Mutual Water Co. #1, San Bernardino Water Utilities Corp.)	Manteca Maramonte Park Marysville Mayfair-Swain Oak Manor (Stockton Vicinity) Mayfair District of Fresno McFarland Meiners Oaks Vicinity (Ventura River Co. Water Dist.) Menlo Park (California Water Service Co.) Merced Midway City Millbrae Mira Loma Miramar Monrovia Montecito Monterey Park Morgan Hill Morro del Mar Mountain View Muscoy (Delmann Water Co.)	Maywood Vicinity Meiners Oaks (Meiners Oak Co. Water Dist.) Menlo Park (O'Connor Tract Co-op Water Co.) Mission San Jose Modesto Vicinity Montclair Montebello (Montebello Land & Water Co., So. Montebello Irrigation Dist.) Monterey Monte Rio Morro Bay	Malibu** Manhattan Beach Martinez Maywood Maxwell Mendota Modesto (City) Mojave Montebello (Park Water Co., San Gabriel Water Co.) Montrose Moorpark Morongo Valley	
Napa Nevada City	North Sacramento North Sacramento Vicinity	Newark New Cuyama	National City-Chula Vista Needles**	

APPENDIX (Continued)

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≤20 mg/L	21-50 mg/L	51-100 mg/L	101-200 mg/L	*201-250 mg/L **>250 mg/L
New Monterey Nice North Highlands North Highlands Vicinity Novato	Norwalk (City, Junior Water Co., County Water Co., Suburban North System)	Newhall Newman Newport Beach Niles North Long Beach Norwalk (Southern California Water Co. "A" System)	Newbury Park Niland Norco North Palm Springs Norwalk (Southern California Water Co. "B" System, Park Water Co.) Nuevo-Lakeview	
Oakdale Oakland Olivehurst Orinda	Oceano Orcutt Orosi Oroville Oroville Vicinity	Oak View Oildale Olive Opal Cliffs Orange Orange Cove Orange Park Acres Oxnard Vicinity (Dempsey Road Mutual Water Co., Vineyard Ave. Acres Mutual Water Co.)	Oakley Oceanside Ojai Oleum Ontario Orland* Oxnard (City)	
Pacifica Pacific Grove Pacific Manor Palm Desert Palm Desert Vicinity (Coachella Valley Co. Water Dist.) Paradise Paradise Park Pebble Beach Country Club Pine Cove Pinedale Placerville Pleasant Hill (E.B.M.U.D.) Pollack Pines Portola	Palm Desert Vicinity (Palm Desert Community Services Dist.) Palm Springs Paramount Vicinity Parlier Pico Piedmont Pinole Pixley Planada Pleasanton Poplar Porterville Portola Valley Princeton-by-the-Sea	Pajaro Palm Springs Desert Paramount Pedley-Sparrland Pismo Beach Placentia Port Hueneme	Pacheco Palmdale Palo Alto Palos Verdes Estates* Pasadena* Paso Robles* Patterson Perris Petaluma Pico-Rivera Piru Pittsburg* Pleasant Hill (California Water Service) Pomona Port Chicago Port Costa	
Rafael Village Rancho Cordova Rancho Cordova Vicinity Redding Redwood City Redwood Estates Rialto Richmond Rio Linda Riverbank Rockaway Beach Rocklin Rohnert Park Ross Running Springs Rutherford	Rancho Mirage Red Bluff Redlands Reedley Rodeo Rosemead Roseville Rubidoux	Quartz Hill Randsburg Riviera Systems East & West (Los Angeles Area) Rosamond	Ramona Rancho Santa Fe Redondo Beach - Hermosa Beach Ridgecrest Riverside Rolling Hills	
Sacramento Metropolitan Area (Oak Park & Parkway Water Co.) Sacramento Vicinity (Citizens Utilities Co., Sacramento Co. Water Agency) St. Helena San Anselmo San Carlos San Francisco San Geronimo	Sacramento (City, Arvin Water Co., Arcade Co. Water Dist.) Sacramento, North (Citizens Utilities Co. of Calif.) Salinas (California Water Service Co.) San Bernardino (City, Baseline Gardens Mutual Water Co.)	Salinas (Pacific Gas & Electric Co.) San Bernardino (East S. B. Co. Water Dist., So. S. B. Co. Water Dist.) San Bruno San Clemente San Jacinto San Joaquin San Jose (S. J. Water Works)	San Diego San Dimas San Fernando San Marino San Miguel Santa Ana (City) Santa Barbara Santa Maria Santa Monica* Santa Paula Vicinity (Limoneira Co.)	

APPENDIX (Continued)

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≤20 mg/L	21-50 mg/L	51-100 mg/L	101-200 mg/L	*201-250 mg/L **>250 mg/L
San Juan Area of Sacramento	San Gabriel	San Juan Capistrano	Santa Susana**	
San Leandro	Sanger	Santa Fe Springs	Santa Susana Knolls	
San Mateo	San Jose (Great Oaks Water Co., White Brothers)	Santa Paula (S. P. Waterworks)	Santa Susana Vicinity**	
San Rafael	San Juan Bautista	Saratoga	Saticoy	
Santa Cruz Vicinity (Santa Hacienda Mutual Water Co.)	San Luis Obispo	Seal Beach	Saugus	
Santa Rosa	San Pablo	Sedco	Seaside	
Sausalito	Santa Ana (So. Main Mutual)	Shafter	Shoshone**	
Sharp Park	Santa Clara	Sierra Madre	Signal Hill	
	Santa Cruz (City)	Soledad	Simi	
		Solvang	Somis-Las Posas	
Shasta Dam Area	Santa Maria Vicinity (Santa Maria Public Airport, Tanglewood)	Sonoma (City)	South Gate (City, So. Calif. Water Co.)	
Sonoma Vicinity (Valley of the Moon Co. Water Dist.)	Santa Ynez	Soquel	South Whittier	
Sonora	Sea Cliff	South San Francisco	Stockton (California Water Service Co.)*	
Springville	Sebastopol	Strathmore	Stratford**	
Stateline	Selma	Sunnyvale	Susana Knolls	
Stockton (Park Woods-Lincoln Village, Colonial Heights Maintenance Dist.)	South Arcadia	Sunset Beach		
Summit City	South Gate (Park Water Co. System)	Susanville		
	South Pasadena			
	South San Gabriel			
	Stanton			
	Stinson Beach			
	Stockton Vicinity (Lincoln Village Maintenance Dist.)			
	Sunnymead			
Tahoe Valley	Taft	Torrance-Wilmington Vicinity (Dominguez Water Dist.)	Thousand Oaks	
Tahoma	Tara Hills	Tracy	Torrance City*	
Talmage Vicinity	Tehachapi	Trona	Tranquility**	
Terra Bella	Temple City	Tulelake	Tri-Cities Municipal Water Dist. (San Bernardino)**	
Thermalito	Temple City Vicinity	Turlock		
Truckee	Thousand Palms	Tustin		
Tuolumne	Tipton	Twenty-Nine Palms		
Twain Harte	Town & Country of Sacramento			
Twain Harte Vicinity	Tulare			
Twin Peaks				
Ukiah		Upland		
Vallejo	Ventura Vicinity (Ventura River Municipal Water Dist.)	Vacaville	Val Verde**	
Vallejo	Victorville	Vista	Ventura-San Buenaventura**	
Valley of the Moon Summer Resort Area	Villa Park		Verdugo City*	
	Visalia		Vernon	
Walnut Creek	Wasco	Watsonville	Walnut Park	
Walnut Grove	Westminster (City-Tract 3003, Dyke Water Co., Orange Co. Water Works, So. Calif. Water Co.)	West Covina	West Sacramento (Washington Water & Light)	
Weaverville	West Riverside	Westminister (City)	Wheatland	
Weed	Willowbrook	West Sacramento (West Sacramento Water Co.)	Whittier (Suburban Water System)*	
West San Bernardino Co. Water District	Wilmar	Whittier (City, Citrus Grove Heights Water Co., Orchard Dale Co. Water District, San Gabriel Valley Water Co.)	Whittier Vicinity (Murphy Ranch Mutual Water Co.)	
Westview	Winters		Williams	
Willits	Woodlake		Woodland	
Winton	Woodside	Willows		
Wrightwood	Woodside Highlands	Woodland		
	Woodville			
Yreka	Yucaipa (San Bernardino Valley Municipal Water Co., Yucaipa Water Co.)	Yorba Linda - Yuba City	Yolo	
	Yucca Valley	Yucaipa (Western Heights Water Co.)		

Atherosclerosis Calls for a New Kind of Preventive Medicine

FREDERICK T. HATCH, M.D., PH.D., *Livermore*

PREVENTIVE MEDICINE has in past years been primarily a function of the sanitary engineer and the health officer, and of the pediatrician and the general practitioner in their practice devoted to mothers and children. Together, the forces of preventive medicine have helped to cut the death rate in the United States from approximately 17 per thousand per annum in 1900 to about 9.5 in 1960 for the white population.¹

An analysis of mortality data, as is well known, reveals that the improvement has come about through the control of many bacterial and parasitic diseases.¹ While this accomplishment has resulted in improved life expectancy below age 45, there has been little gain above that age (Chart 1), where chronic cardiovascular disorders due to atherosclerosis and malignant neoplasms have become the major causes of death (Table 1). So far no substantial improvement in mortality from these disorders has occurred; and the United States ranks below many countries in the life expectancy of men at age 45 (Table 2). In fact, in recent years morbidity and disability from these diseases have even increased and there has been a tendency for complications of atherosclerosis to develop in still younger people.^{1,a}

Atherosclerosis will be the principal or a major contributing cause of death in about 50 percent of all people now living in the United States and in many of the other developed nations. Thus it is the greatest public health problem today. Nearly all adult human beings have this condition to some degree. Yet we are still unable to determine the extent or rate of development of the disease until obstruction of the blood flow threatens some vital

organ and produces obvious symptoms or sudden death.

New therapies for the complications of atherosclerosis have a limited relevance to its control. Improvements in resuscitation and intensive care techniques, and surgical approaches via transplantation, prosthesis and the like will salvage a certain number of people who would otherwise die or be disabled by atherosclerosis. However, these measures are only of a stop-gap nature; they have nothing to do with the mechanism of progress of the disease or with its prevention. Approximately one-fifth of persons in whom myocardial infarction occurs die at the first occurrence before obtaining definitive medical care in a hospital⁶; the proportion may exceed one-half for men below 50 years old.⁷ Only preventive measures can benefit these people.

Atherosclerosis calls for a new kind of preventive medicine. The science and techniques of sanitation, vaccination and chemotherapy that were so successful in improving the outlook for the younger members of our population over recent decades have not yet been replaced with the tools needed for today's major problem. A program of individualized preventive medicine is proposed for apparently healthy people who have a high risk of complications of atherosclerosis. Such a program requires grass-roots participation by individual clinicians, aided by many paramedical professions, to reach and work with all people at risk in the community. Preventive medicine of this new type is by no means a simple or cut-and-dried matter. Further research by government and medical schools will be required to define and assess the effectiveness of preventive measures. But a serious need exists now and demands the attention of as many physicians as possible.

From the Bio-Medical Division, Lawrence Radiation Laboratory, University of California, Livermore.

Reprint requests to: Bio-Medical Division, Lawrence Radiation Laboratory, University of California, Livermore, 94550.

TABLE 1.—Major Causes of Death in the United States
(Data for both sexes 45-54 years of age. Total U.S.
population in the age range approximately 21 million.)

	Estimated Deaths in 1962 (4, p. 15)
Arteriosclerotic Heart Disease	45,000
Cerebrovascular Accidents	10,000
Hypertensive Heart Disease	4,200
Cancer	37,500

Individualized Preventive Medicine— The Program

Who Needs Protection? The Risk Factors.

The program of preventive medicine for atherosclerosis will be presented as if it pertained to subjects who still appear to enjoy good health. However, the remarks generally will be applicable to persons with manifest complications of atherosclerosis who are not seriously disabled.

Characteristics have been sought which distinguish the susceptible members of the population from others of similar age in whom the risk of coronary heart disease is much lower. Identifying risk factors is a difficult task. While a perfect epidemiological study or clinical experiment is yet to be carried out, nevertheless several well-designed studies have produced findings, similar one to the others. Both retrospective comparisons of

TABLE 2.—Life Expectancy for Men at Age 45
in Various Countries
(Data From Approximately 1960⁵)

Rank	Country	Average Years Remaining
1	Sweden	29.9
2	Canada	28.5
3	Italy	28.1
4	U.S.S.R.	28.0
5	Mexico	27.3
6	France	27.1
7	United States	27.0
7	Great Britain	27.0
9	Japan	26.8
10	Egypt	26.4

patients recovered from myocardial infarction with appropriate healthy controls,^{8,9} and elaborate prospective studies of presumed healthy populations have identified the features distinguishing those in whom coronary heart disease develops.^{6,10,11,12} From these studies we may conclude: (1) that about a dozen risk factors can be identified, (2) that the risk factors are present before overt complications occur, and (3) that the presence of multiple risk factors has an additive effect on risk. One may now assume that, taken in combination, these factors provide a fairly accurate index, for the individual, of his risk of coronary heart disease. The use of risk factors should be familiar to most physicians, for they utilize some form of statistical appraisal consciously or unconsciously in their daily practice for deciding the alternatives of diagnosis or treatment.

Age Factor

The studies show that the risk factors are more definite indicators for men below age 50 or 55 years. Beyond age 55 the differences become smaller or undetectable, in part perhaps because of selective removal of those with major abnormalities before they reach middle age.

Hereditary Factors

Atherosclerosis develops as a result of complex interactions between a variety of factors and the hereditary background or genotype of the individual,^{9,10} (Chart 2). Although manipulation of the genotype of a subject is not yet within our capabilities, the family history of cardiovascular disorders is an important indicator of risk.^{9,13,14} The family history is probably a strong reflection of the genotype, with additional contributions from similarities of environment and culture among family members. The genotypic mechanism may involve the strength and reserve capacity of meta-

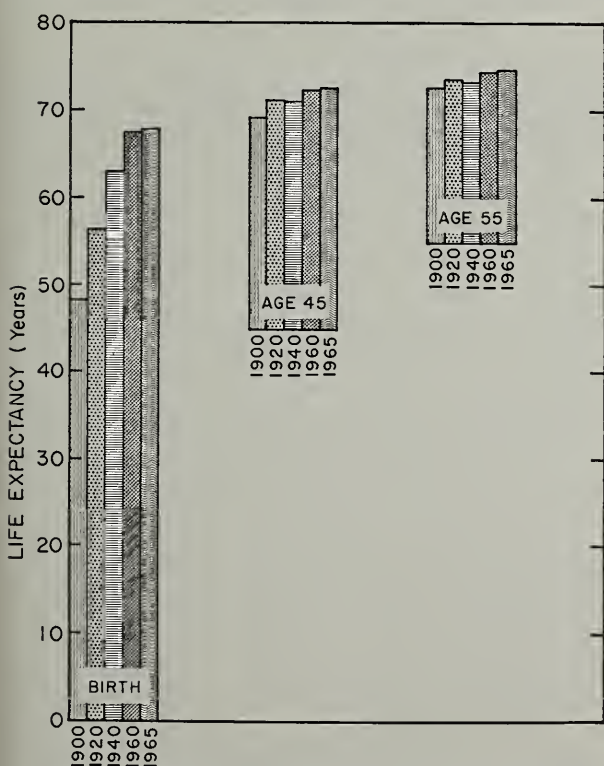


Chart 1.—Life expectancy of white males in the United States at intervals since 1900.^{2,3}

GENETIC FACTORS

ENVIRONMENTAL FACTORS

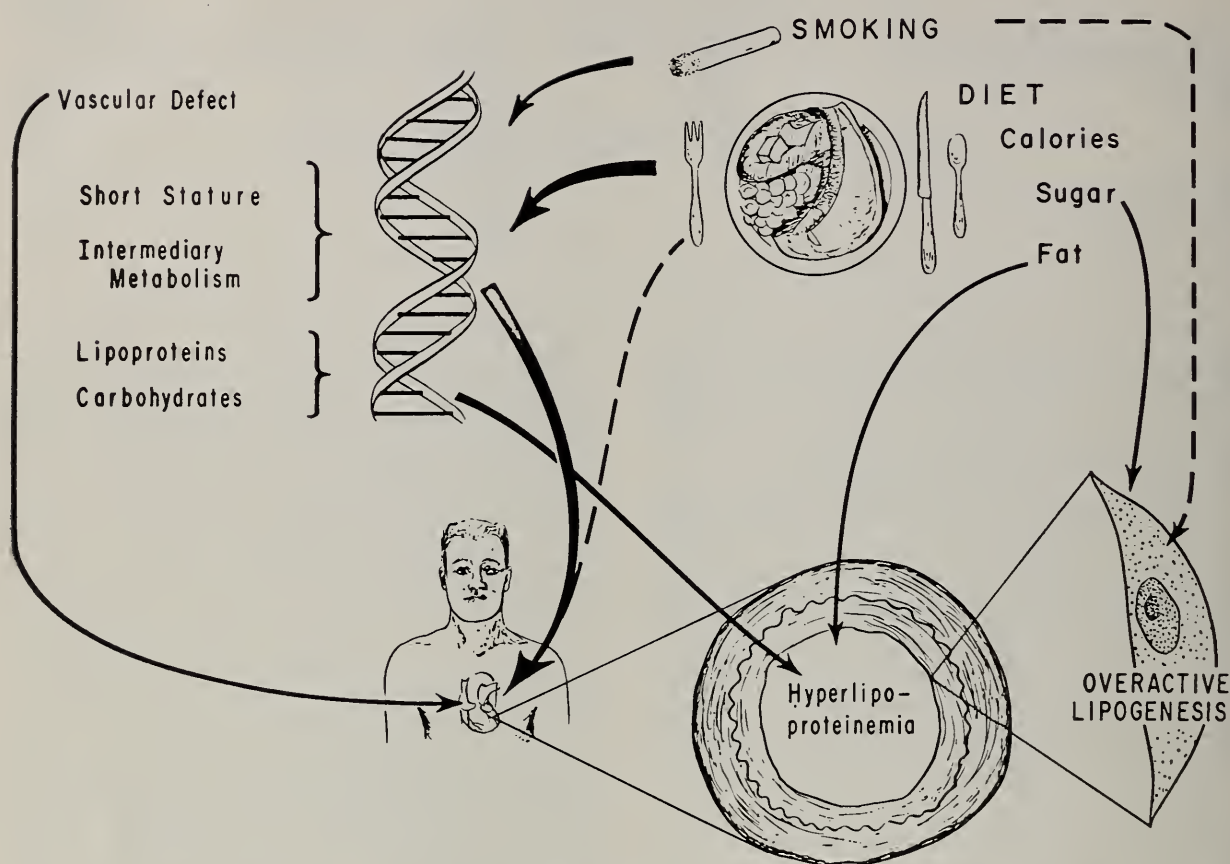


Chart 2.—Schematic representation of the complexity of the environmental and hereditary influences which may accelerate the progress of human atherosclerosis. The incriminated environmental factors are thought to play their role largely through interactions with genetically determined pathways of intermediary metabolism and properties of arterial tissue. (Reprinted with permission of the American Heart Association from Hatch.⁹)

bolic and other pathways for coping with stresses applied by the person or his environment. In evaluating the total risk of an individual it seems probable that one should weigh other risk factors in proportion to the incidence of atherosclerosis complications in the family.

One risk factor that seems likely to be hereditary is short stature.^{9,13} A significantly higher risk of both myocardial infarction and strokes applies to persons less than 5 feet 8 inches tall.

Personal Factors

Characteristics of Personality. A personality type characterized by highly competitive drive and a concern with urgency of time is associated with an increased risk of coronary heart disease.^{15,16,17} Evaluation of these personality characteristics has heretofore required a skilled interviewer, but re-

cently a promising objective test has been devised.¹⁸

Overnutrition. A prominent feature of our way of life is the presentation of large loads of food-stuffs to the body at infrequent intervals. The actual needs for these substances for energy or for anabolic purposes are on a different time schedule, and often the total need is for much less than the amount ingested. Temporary disposition of products derived from food ingestion is therefore required, and the mechanisms for coping with the overload may lead to increased plasma lipoproteins and impaired glucose tolerance. The correlation between overnutrition or overweight and coronary heart disease has varied in different studies. In the Framingham study only gross obesity appeared to be a significant risk factor.^{6,19} On the other hand, in a study in my laboratory of young

men with coronary disease and age-matched controls, gross obesity was absent and both series averaged 10 percent above ideal weight for their height.⁹ However, intercorrelations of metabolic factors were observed which led to the speculation that in genetically prone persons overnutrition could be significant, perhaps by contributing to the metabolic risk factors.^{9,20}

Exercise. The role of lack of exercise as a risk factor in coronary heart disease is supported by a variety of studies.^{21,22} In nearly every case the evidence was confounded by lack of valid data on the actual energy expenditures in occupational or recreational pursuits and by other dissimilarities in the populations—for example, smoking habits and social class. Making the best of this, one may probably conclude that the incidence of coronary heart disease is inversely proportional to the level of physical activity. However, evidence is lacking that the extent of atherosclerosis is correlated with physical activity. The relationship is rather that lack of exercise is associated with overt complications. A more forceful result was obtained in a study of the mortality soon after an initial clinical episode.²³ When subjects were rated for both occupational and outside activities there was a fivefold difference in mortality within the first 30 days, the rate being least among the most active.

Cigarette Smoking. The importance of heavy cigarette smoking as a risk factor in coronary heart disease and in cerebrovascular accidents is statistically established.^{13,24} Although a causal relationship has not actually been proven,²⁵ a recent revision of the *Surgeon General's Report on Smoking* strengthens the affirmative case greatly.²⁶ The extent of atherosclerosis, the incidence of complications and the mortality associated with them have all been found to be promoted in considerable degree by cigarette smoking.^b Smoking may act indirectly through the genotype or through influences on metabolic factors, the blood coagulation system or the sympathetic nervous system.

In studies in my laboratory of 24 men between 23 and 49 years of age with proven myocardial infarction, all patients were heavy cigarette smokers, except one who was a former smoker; they averaged 1.9 packages per day in contrast to one package a day in the age-matched controls.⁹

Clinical and Metabolic Observations

Blood Pressure. The blood pressure has uni-

formly been found to be a highly significant risk factor in coronary heart disease,⁶ and especially in cerebrovascular accidents.¹³ Actuarial experience and epidemiological studies show that there is no threshold of abnormal blood pressure and that the risk of complications is more or less linearly proportional to the blood pressure throughout its range.

Electrocardiogram. There is no agreement among investigators on the significance of minor electrocardiographic abnormalities as risk factors for the development of coronary heart disease. Probably they signify occult impairment of the coronary circulation, and therefore are more a sign of impending complications than a risk factor of early value. Recently the application of exercise stress in conjunction with electrocardiography has been advocated for improved risk evaluation.²⁷

Serum Cholesterol. The serum cholesterol level has been shown to increase with age over the early and middle range of life, so that any discrimination between persons at high and low risk must take age into consideration. However, at ages below 55 years there is no threshold of abnormality, but a continuous increase in risk from the lowest to the highest serum cholesterol levels.^{6,10} In men in the fourth and fifth decades a higher level of risk is clearly detectable at serum cholesterol levels above only 210 mg per 100 ml.

Fasting Serum Triglycerides. Because of difficulties in chemical measurement, the triglyceride level has only recently been recognized as a risk factor. Elevated fasting serum triglycerides are commonly found in persons who are overnourished and have gained substantial weight during adult life (as distinguished from childhood obesity).^{28,29} Although elevations of triglycerides are commonly associated with elevated serum cholesterol, the former probably serve as a risk factor in their own right, particularly in young men.³⁰⁻³²

Abnormal Serum Lipoprotein Levels. Inasmuch as all the plasma lipids are transported in the form of lipoproteins, various measures of these macromolecules have been useful in evaluating risk. The technique of examination of lipoproteins in the analytical ultracentrifuge was described and utilized by Gofman and his associates more than 15 years ago.³³ However, the difficulty and expense of the technique have made it relatively unavailable for clinical investigation even in research centers. A modified paper electrophoretic technique has provided simple qualitative demonstra-

TABLE 3.—*Prevalence of Risk Factors in Men**

Study	Ref.	No. of Men	Age Range at Start Years	Abnormal				Summation		
				Blood Press.	Serum Chol'rol	Body Weight	Cigarette Smoking Percent of Men	All Fav'ble	Not Abnor.	Two or More Abnor.
Framingham, Mass.	6	1350	40-59	22	32	9	47	9	49	12
Chicago, Ill.	39	1466	40-59	10	28	29	42	7	..	13
Chicago, Ill.	40	1870	40-55	18	38	..	39	25
Minnesota	41	300	45-55	5	20	12
Evans Co., Ga.	42	656	40-74	32	24	..	15	28	53	9
Tecumseh, Mich.	43	2372	> 16	20	20	28
National Diet-Heart Study..	44	2032	45-54	..	20	36	26	13

* Because data from the cited studies are not expressed in equivalent terms, certain liberties were taken in compiling this table. The boundaries for abnormality were not identical, but for each study values above the selected boundary were shown to be associated with an increased risk of having or developing coronary heart disease.

tion of the various serum lipoproteins suitable for diagnostic purposes.^{34,35} More recently semi-quantitative measurements of the fractions have been made so that numerical data may be obtained.³⁶ The principal findings relative to coronary heart disease and cerebrovascular disease have been elevation of very low density (electrophoretic pre-Beta) lipoprotein, elevation of Beta-lipoprotein, and decreased Alpha₁-lipoprotein.⁹ Since the pre-Beta-lipoprotein and Alpha₁-lipoprotein are frequently inversely related to each other, it is not yet certain whether the depression of Alpha₁-lipoprotein contributes independently as a risk factor.

Abnormal Glucose Tolerance. A mild abnormality of the glucose tolerance test is associated with coronary heart disease.^{9,37} This has been considered by some investigators to indicate that coronary heart disease is highly prevalent among persons with unrecognized mild diabetes in the population, in addition to its frequency in overtly diabetic patients. The evidence from studies in my laboratory, though not conclusive, favored the idea that the abnormal glucose tolerance is not directly related to diabetes mellitus, but is a separate risk factor related to overnutrition in persons with an appropriate genotype.^{9,20}

Other Biochemical Abnormalities. Other biochemical measurements such as elevated uric acid⁸ and hematocrit³⁸ have been thought to represent additional risk factors. Abnormal values of either measurement have not been consistently indicative of risk.

Prevalence of Risk Factors. Variations in Risk.

The prevalence in study populations of several risk factors is presented in Table 3. The data show that factors associated with the presence or development of coronary heart disease are frequently present in supposedly healthy populations, and

that perhaps 10 percent of the population exhibits at least two of the unfavorable items (see also references 45-47). Since some of the studies in Table 3 comprised health-conscious volunteers, the data may underestimate the true prevalence of some risk factors.

Coronary heart disease develops in about 0.5 percent of men per year in the fifth decade and about 1 percent per year in the sixth decade.⁴⁸ If this incidence is extrapolated over a 20-year period of middle age, then the male population in general has nearly one chance in five of having the disease in middle life. The epidemiologic data show that for those in whom all of the risk factors are low—in the favorable range—the risk decreases to one chance in 20 to 40. However, the presence of two or three of the abnormal risk factors, even though none are extreme, increases the risk to at least one chance in two—a 50:50 probability.^{45,49} Such a man is clearly marked for trouble ahead unless some preventive measures can be brought to bear.

What Preventive Measures Can Be Applied?

Cigarette Smoking. Cessation of cigarette smoking or at least reduction to a level below ten cigarettes a day is probably the most clearly indicated measure in a preventive program for atherosclerotic complications. The experience since publication of the Surgeon General's reports on smoking shows that cessation will be one of the most difficult measures to achieve. However, encouraging reductions among physicians and young adults have occurred. Favorable results have been achieved by a physician's routine admonition against smoking.⁵⁰ Nothing must be permitted to blunt the effort to achieve reduction in what is probably one of the strongest contributors to cardiovascular disease.

Diet. Individualized management is especially important in diet control. The nutritional history of the subject and the nature and magnitude of the metabolic abnormalities should be considered in deciding the role of diet therapy. The primary objective should probably be the consumption of calories that will first direct the individual toward his ideal body weight, and then maintain him as close to that level as possible. Any weight gained after attainment of adult life should be eliminated if practicable. Weight loss due to simple caloric deprivation will often correct sizable abnormalities in the serum lipid and lipoprotein levels. However, if the lipoprotein abnormalities are prominent, modification of the fat and carbohydrate content of the diet should be undertaken. In brief, reduction of elevated serum cholesterol levels is best accomplished by partial substitution of polyunsaturated for saturated fats in the diet and a decrease in dietary cholesterol⁵¹; and reduction of elevated triglyceride levels is best achieved by reduction of calorie and/or carbohydrate intake.⁵² Palatable diets have been devised and have been utilized satisfactorily by properly motivated patients and physicians over long periods. As is true of cigarette smoking, diet modification is difficult to achieve in apparently healthy persons. But if the high risk persons are well-informed about the need and how to meet it, there will be favorable results.

Exercise. Experiments in dogs show that exercise promotes the development of collateral circulation in the heart when the main vessels are impaired.^{53,c} There is evidence in man that physical activity may postpone for some years the development of the clinical manifestations of atherosclerosis; and this may be due in part to improved collateral blood supply.²¹ Nutritional status, diet and exercise are closely interrelated, and an appropriate balance among them is best achieved by considering them together.

Exercise, therefore, should have a role in the management of high risk persons—indeed, perhaps all individuals. Its benefits may lie not only in the circulatory effects, but also in aiding the correction of overnutrition, hyperlipidemia and disorders of carbohydrate metabolism.

The prescription of appropriate exercise regimens is a complex subject, which has been well discussed by Fox and Skinner²¹ and by Mayer.²² Properly managed, they are without appreciable

risk even for many patients who already have one or more clinical complications.

Way of Life. Although difficult, it is within the physician's capability to evaluate his patient's way of life and to recommend changes which might bring possible harmful factors under control. The essence of preventive management is a coordination of diet, exercise, vocation and avocations, together with an effort to eliminate cigarette smoking. Surprisingly, advice in these matters is often welcomed by the recipient.

Drugs. It is beyond the scope of this paper to discuss pharmacologic preventive measures. Indeed, these are under intensive evaluation in a number of cooperative programs going on throughout the world.^{54,55} In the present context, drug therapy is an adjunct to nutritional therapy in the correction of biochemical risk factors. After the disastrous false start in this field a few years ago with triparanol, in which delayed and serious side effects completely negated any possible benefits, caution is essential. At present the drug chlorphenoxisobutyrate appears to show promise and safety, and there are several other agents—for example, estrogens, nicotinic acid, d-thyroxine and cholestyramine resin under study.⁵⁴ Treatment of hypertension with drugs is better established.

Will the Preventive Measures Help?

It would be futile to advocate a new and difficult kind of preventive medicine if there were not a reasonable expectation of benefit, but it must be admitted that we do not yet completely know whether the preventive measures will help. Considerable evidence supports the affirmative. During the time it will take to establish the approaches recommended in this article, better information will become available from a number of large scale human experiments now being conducted throughout the world.

Under the conditions of clinical investigation, dietary and pharmacologic measures can achieve a consistent lowering of serum cholesterol and other lipids.^{51,54} In the case of persons with only slight elevations, the usual result is a diminution of approximately 10 to 15 percent in the serum cholesterol level. More recently, data have become available from the pilot project of the National Diet-Heart Study⁴⁴ and the Coronary Drug Project⁵⁵ which indicate that similar control of serum cholesterol level can be achieved by diet and drugs in moderately large numbers of free-

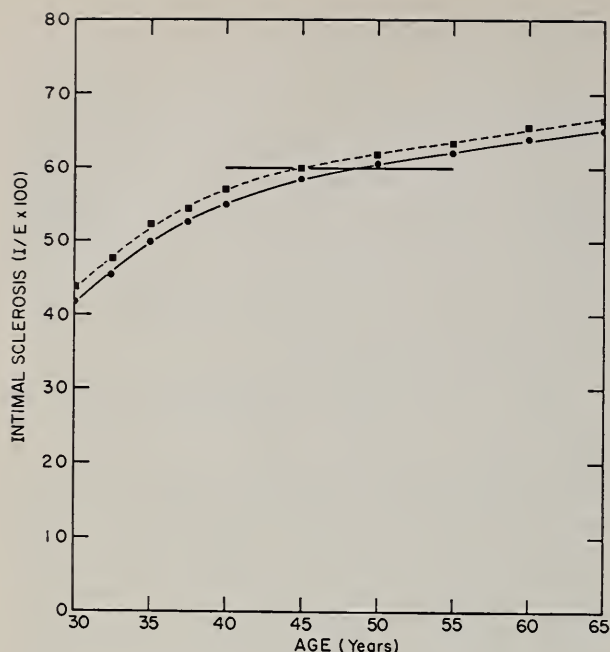


Chart 3.—Diagram, modified from Reference 56, Figure 3, based upon Gofman's model of the relationships among age (abscissa), a serum lipid parameter (curves) and the degree of atherosclerotic involvement of the coronary arteries (ordinate). Solid curve is for population median serum lipid level; dashed curve is for 17 percent higher lipid level. Horizontal line at $I/E \times 100 = 60$ is at a degree of sclerosis postulated to lead to clinically evident coronary heart disease. A 17 percent reduction of the lipid level throughout middle age might delay by three to four years attainment of the danger threshold for heart disease.

living Americans. Reasonable evidence exists that control of one of the major risk factors, hypercholesterolemia, can be achieved by various means.

If an important risk factor such as the serum cholesterol level can be reduced significantly, what would be the effect on morbidity or mortality from coronary heart disease? Gofman recently presented a theoretical model which was based upon experimental and epidemiological evidence.⁵⁶ This model is based upon the premise that the total amount of intimal atherosclerosis is related to the product of a serum lipid level (cholesterol in the simplest case) and time. In early adult life the amount of intimal atherosclerosis will be highly dependent upon the level of the serum cholesterol. After age 50, however, when atherosclerosis is advanced in most people, there will be relatively little dependence upon cholesterol level, and there will be little further increase in atherosclerosis with age.

Gofman predicted from his model that while a moderate reduction of serum cholesterol might

significantly lower the risk of coronary heart disease below age 55, the effect would be lost in the older age groups; in the latter only a drastic reduction in cholesterol level over many years would produce a significant decrease in risk. However, inspection of a diagram based on the model (Chart 3) suggests that a reduction of about 17 percent in serum cholesterol from an initial level somewhat above the median, might delay by about three or four years the attainment of a given degree of atherosclerosis. Of course, the numerical estimate is only an approximation from the model, but there seems to be no definite upper age limit to this potential postponement. We have seen that 17 percent is an achievable degree of serum cholesterol reduction, and conclude that a few years' delay in reaching a dangerous amount of coronary atherosclerosis is a worthwhile objective.

In a separate discussion,⁵⁷ Gofman considered the preliminary report of the International Atherosclerosis Project.⁵⁸ The relevant feature of this report was that the extent of atherosclerosis in persons who died of coronary heart disease was very similar in both sexes, in many age groups and over a wide variety of geographic locations and races. Gofman's mathematical analysis of this finding suggests that the clinical complications of atherosclerosis, particularly coronary heart disease, become evident at some unknown, but fixed, degree of coronary atherosclerosis. Therefore, among populations varying widely in the average extent of atherosclerosis, and perhaps in serum lipid factors, it would be predicted that those persons in whom complications developed had about the same amount of atherosclerosis.

Returning to Gofman's first model, we note that if there is a particular amount of atherosclerosis which serves as a threshold for clinical complications, then any measure such as serum lipid reduction which could delay attainment of the threshold level would effect a desirable decrease in the incidence of complications.

Cornfield analyzed the data of the prospective study of coronary heart disease in Framingham, Massachusetts, after six years.⁵⁹ The risk of developing the disease was proportional to the serum cholesterol level raised to an exponent between the square and cube. This simply means that the risk from cholesterol elevation accelerates rapidly as the level rises. Recently, Frantz tested this mathematical relationship on data from other epidemiological studies and found reasonable

TABLE 4.—*Observed Reduction in Coronary Heart Disease with Cholesterol Lowering by Dietary Treatment*

Investigator	Ref.	Population	No. of Men	Age Range at Start Years	Duration Years	Change in Serum Cholesterol Percent	Change in Risk of CHD Percent	Signif. of Risk Change (P)
Leren	61	Survivors of MI	216	30-67	5	-14	-33	.01
Christakis, <i>et al.</i>	62	Healthy men of high risk	814	40-59	7	-9	-65	<.01
Bierenbaum, <i>et al.</i>	63	Survivors of MI	100	20-50	5	-9	-38	<.01
Turpeinen	64	Mental patients	313	35-64	6	-18	-56	<.01

agreement with the original relationship (serum cholesterol exponents varying from 1.7 to 5.5).⁶⁰ He then made use of this relationship to *estimate* the effect upon the incidence of coronary heart disease that might have occurred in the presence of a 15 percent reduction in mean serum cholesterol level in the populations. The calculated reduction in risk of the development of new coronary heart disease ranged from 25 to nearly 60 percent. This effect upon risk is substantial, although of course data from population studies cannot predict directly the effect of a reduction in cholesterol level upon risk in a particular individual; and there is so far only preliminary evidence that a reduction in risk would actually follow.

Preliminary data bearing upon this important question are now available. There are four studies in which statistically significant decreases in coronary heart disease morbidity or mortality in middle-aged men have been achieved⁶¹⁻⁶⁴ (Table 4). In these studies dietary changes resulted in decreases in serum cholesterol level ranging from 9 to 18 percent in experimental groups of from 100 to 800 men over periods of five to seven years. The decrease in risk of developing new or recurrent coronary heart disease ranged from 33 to 65 percent. None of these studies is definitive, all have been criticized from some point of view, and some of them are still in progress. However, they give a consistent answer, which is that there is a good possibility that dietary management can lower the serum cholesterol level and substantially diminish the risk of developing coronary heart disease. These experiments stand as the principal justification of a program of individualized preventive medicine.

Individualized Preventive Medicine—Implementation

Finding the Susceptible Persons

In previous sections we have indicated the characteristics which identify persons at a higher than average risk of acquiring the complications of atherosclerosis; we have outlined the preventive

measures that could be applied to lower the risk; and we have presented preliminary evidence that application of the preventive measures would be successful. The first important step in implementation is finding the susceptible persons in the population. They will be for the most part healthy persons who are not actively seeking medical care. Therefore, they must be sought for through general health surveys and through public health education, which will point out that some persons are at high risk, and that help in reducing that risk is available.

The medical profession may become involved in this identification process in many ways. First, the general physicians, through their practice of family medicine, should take an interest in the healthy as well as the sick members of the families under their care and promote examination of the healthy. This applies especially to the young and middle aged men. Second, the physicians participating in industrial, union and college health programs and in prepaid health plans can make contact with otherwise healthy persons and evaluate risk factors as part of their regular functions. Military physicians also deal with a large population of the susceptibles. Finally, the life and health insurance companies should have a sufficient financial as well as humanitarian interest to require their clients to submit to an evaluation of risk factors and, if necessary, to be referred for preventive management.

Measuring the Risk

How may the risk of developing cardiovascular disease be evaluated simply, inexpensively and with the least inconvenience to subject and physician? As described above, the risk factors include hereditary background, nutritional history and personal habits, as well as objective clinical and metabolic observations. The family history and personal habits can be evaluated by objective questions upon written forms amenable to processing by computer. Nutritional information may require the help of a dietitian or nutritionist. However, the

measurement of body weight and height and comparisons with the figures at 20 years of age will provide the most relevant information.⁶⁵ The biochemical evaluation also need not be alarming or expensive. Serum cholesterol determinations have been automated and are widely available.⁶⁶ Determination of serum triglycerides is less available, but is performed by automation in some laboratories.⁶⁷ Evaluation of serum lipoproteins by electrophoresis is simple and inexpensive.^{34,36,68} Finally, a screening glucose tolerance test may be performed in non-fasting persons by the feeding of a standard dose of glucose followed in one hour by a single blood glucose determination, also by automated methods.^{37,69}

The evaluation of total risk is properly the function of a physician. It is not difficult to add up the number and magnitude of risk factors, but these values probably cannot yet be reduced to a simple numerical scale. Someone with judgment and understanding must evaluate the situation and carry out at least a short interview with the subject.

Prescribing a Preventive Program

The effective reduction of risk factors in susceptible persons will not be a simple matter, for it involves the modification of established habits of those who believe themselves to be in good health. Further, long-term observations and reinforcement will be required. One has only to consider how limited the success of traffic safety programs and anti-smoking campaigns to recognize the difficulty of instituting another program of this general type. There is a serious need for research in the behavioral sciences to help us understand how habits are formed and how they can successfully be modified.

Probably no one knows how best to proceed. Some of my suggestions are rational, others perhaps heretical; some measures are obviously feasible, others may prove impractical. One cannot decide from theory how this program can be made to work. I believe trial-and-error experimentation is the way to proceed.

From whatever point the subject deemed to be at high risk is identified, he should be referred to a physician who is preferably his personal choice. However, a successful management program can also be carried out as part of the health services of industry, unions, welfare agencies, educational institutions and the like. The physicians concerned, including those in private practice, will need much

assistance from the paramedical professions. The most obvious needs are for laboratory technicians, dietitians or nutritionists, nurses and psychologists.

How to Make the Program Work

Health Education. From a long-range viewpoint health education in our elementary and secondary schools can mold attitudes and behavior in children about overweight, exercise and smoking which will help to prevent the development of many risk factors.

Community Programs. Local health and welfare agencies and the voluntary heart associations can disseminate reliable health information to children and adults and can sponsor surveys for detection of high risk individuals.

Mass Media. Advertising and educational programs via mass media need further exploration. The skillful use of television probably has no equal for informing the public and influencing their behavior. However, we do not yet know whether a successful presentation should emphasize information content, instill fear or approach the wives of the men who are at risk.

One important function of these programs is the creation of consumer demand for detection surveys, management clinics, modified food products and the like. Consumer interest can be much more effective than legislative or administrative direction in achieving some of the new objectives.

Group Therapy. Various forms of group therapy such as are used for alcoholism, obesity and cigarette smoking need to be tried.

Rehabilitation Centers. Elsewhere in the world so-called "rehabilitation centers" have become popular—where people who need it can take a health-oriented vacation under conditions in which medically indicated measures are provided without the expense and atmosphere of a hospital.⁷⁰

Modified Foods. The cooperation of the food industry is needed to make generally available some of the modified foods used in the National Diet-Heart Study.⁴⁴ In that study the total fat content and the proportion of polyunsaturated fatty acids in certain important food items were altered without sacrifice of taste acceptability or nutritional value.

Rewards for Compliance. Life and health insurance companies might offer reexamination at intervals. Discounts might be given for cessation of smoking and improvement of other factors

through preventive management, as is already the case for control of blood pressure and body weight. Actuarial data confirm the soundness of the present practice. Additional interest in the risk factors on the part of insurance companies is economically sound for them, and an invaluable source of statistics on the results of preventive management would be provided if followup examinations of high risk individuals were carried out.

Penalties for Non-Compliance. Life and health insurance carriers might assess penalties for risk factors, in addition to those now assessed for excessive blood pressure and body weight.

When we receive, from studies now in progress, further assurance that preventive management is feasible and effective in reducing risk, adherence to the program by susceptible persons might be made a condition for promotion or achievement of tenure in industrial, unionized or military activities. The economic and social burdens of death and disability due to coronary heart disease justify this seemingly severe argument.

The Physician's Example. The personal example set by the physician and his family with respect to smoking, control of body weight and hygienic exercise is important. People become aware of the physician's faith in his recommendations to them through observing his own behavior. Already physicians appear to have taken the lead with a substantial reduction in cigarette smoking. There is an incentive for physicians to become personally involved in this program because *they* are highly vulnerable to coronary heart disease.

Individualized Preventive Medicine—Potential Benefits

The total mortality from coronary heart disease in the United States is 550,000 per year (about 200,000 per year are below age 65); from cerebrovascular accidents, 200,000 per year (80 percent over age 65).^{71,p.3} These diseases affect between 2 and 4 percent of the total population (prevalence).^{4,p.22} The economic loss from mortality and disability is estimated to be 1 percent of the Gross National Product (*about 7 billion dollars in 1962*).^{4,pp.449-460} Achievement of even a modest reduction in incidence and mortality would be of inestimable value. A 30 percent reduction would add 2.4 years to the life expectancy of males at age 45—twice the amount added between 1920 and the present (Table 5).

The atherosclerosis problem is at a crossroads,

TABLE 5.—Potential Gains in Longevity from Reductions in Certain Death Rates (1964 Data for White Males⁷²)

Present Age (years).....	45	55	65	
Present Life Expectancy (years)...	27.1	19.3	12.9	
	<i>Reduction in Death Rate</i>	<i>Added Life Expectancy (years)</i>		
Cardiovascular-Renal Disease	10%	0.7	0.7	0.6
	30%	2.4	2.2	2.0
Malignant Neoplasms	10%	0.2	0.2	0.2
	30%	0.6	0.6	0.65
Accidents	10%	0.05	0.03	0.02
	30%	0.14	0.10	0.07

from which the roads to a practical solution and to a real understanding may diverge. Even though the pathogenesis of atherosclerosis is still not fully understood and further research along many lines is needed, we can today recognize susceptible persons and apply preventive measures which are inexpensive, safe, and not seriously onerous. These measures have a good prospect of being at least moderately successful. The preliminary results summarized in Table 4 show that a 30 percent reduction in incidence is by no means too much to hope for.

The new kind of preventive medicine that I have proposed is required to gain the upper hand over today's major public health problem. The new approach can be carried out most effectively by a partnership among physicians, the paramedical professions, public health officials, and government—by the formation of a cooperative enterprise that has not hitherto been a part of medical practice. The physician is the pivot of this interaction between medical care and individual members of the public. He must add a new role in the conservation of health to his traditional role in restoring the health of the sick.

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REFERENCES

1. U.S. National Center for Health Statistics: The change in mortality trend in the United States, Public Health Service Pub. No. 1000, Series 3—No. 1, Washington, D.C., Mar. 1964.
2. Metropolitan Life Ins. Co., New York, N.Y.: Progress in longevity since 1850, Statistical Bulletin, 44:1, July 1963.
3. Metropolitan Life Ins. Co., New York, N.Y.: Longevity relatively unchanged, Statistical Bulletin, 48:8, Aug. 1967.
4. National Program to Conquer Heart Disease, Cancer and Stroke (Report to the President), Vol. II, Feb. 1965, p. 15.
5. Metropolitan Life Ins. Co., New York, N.Y.: International gains in longevity after midlife, Statistical Bulletin, 45:1, Apr. 1964.

6. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N., and Stokes, J., III: Factors of risk in the development of coronary heart disease—six-year follow-up experience. The Framingham Study, *Ann. Intern. Med.*, 55:33, 1961.
7. Bainton, C. R., and Peterson, D. R.: Deaths from coronary heart disease in persons 50 years of age and younger. A community-wide study, *New Eng. J. Med.*, 268:569, 1963.
8. Gertler, M. M., and White, P. D.: *Coronary Heart Disease in Young Adults—Monograph*, Harvard University Press, Cambridge, Mass., 1954.
9. Hatch, F. T., Reissell, P. K., Poon-King, T. M. W., Canellos, G. P., Lees, R. S., and Hagopian, L. M.: A study of coronary heart disease in young men. Characteristics and metabolic studies of the patients and comparison with age-matched healthy men, *Circulation*, 33: 679, 1966.
10. Kannel, W. B., Dawber, T. R., Friedman, G. D., Glennon, W. E., and McNamara, P. M.: Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease. The Framingham Study, *Ann. Intern. Med.*, 61:888, 1964.
11. Epstein, F. H.: The epidemiology of coronary heart disease. A review, *J. Chron. Dis.*, 18:735, 1965.
12. Friedman, G. D., Kannel, W. B., Dawber, T. R., and McNamara, P. M.: Comparison of prevalence, case history and incidence data in assessing the potency of risk factors in coronary heart disease, *Amer. J. Epidemiol.*, 83:366, 1966.
13. Paffenbarger, R. S., and Williams, J. L.: Chronic disease in former college students. V. Early precursors of fatal stroke, *Amer. J. Public Health*, 57:1290, 1967.
14. Deutscher, S., Epstein, F. H., and Kjelsberg, M. O.: Familial aggregation of factors associated with coronary heart disease, *Circulation*, 33:911, 1966.
15. Rosenman, R. H., and Friedman, M.: Behavior patterns, blood lipids, and coronary heart disease, *JAMA*, 184:934, 1963.
16. Syme, S. L., Hyman, M. M., and Enterline, P. E.: Some social and cultural factors associated with the occurrence of coronary heart disease, *J. Chron. Dis.*, 17:277, 1964.
17. Friedman, M., Rosenman, R. H., Straus, R., Wurm, M., and Kostich, R.: The relationship of behavior pattern A to the state of the coronary vasculature. A study of 51 autopsy subjects, *Amer. J. Med.*, 44:525, 1968.
18. Bortner, R. W., and Rosenman, R. H.: The measurement of pattern A behavior, *J. Chron. Dis.*, 20:525, 1967.
19. Kannel, W. B., LeBauer, E. J., Dawber, T. R., and McNamara, P. M.: Relation of body weight to development of coronary heart disease. The Framingham Study, *Circulation*, 35:734, 1967.
20. Hatch, F. T.: Some correlations between relative body weight and lipid metabolism parameters in Cowgill, G., and Kinsell, L. W., Eds. 1967 *Deuel Conf. on Lipids*, Public Health Service Pub. No. 1742, p. 233 ff.
21. Fox, S. M., III, and Skinner, J. S.: Physical activity and cardiovascular health, *Amer. J. Cardiol.*, 14:731, 1964.
22. Mayer, J.: Nutrition, exercise and cardiovascular disease, *Fed. Proc.*, 26:1768, 1967.
23. Frank, C. W., Weinblatt, E., Shapiro, S., and Sager, R. V.: Physical inactivity as a lethal factor in myocardial infarction among men, *Circulation*, 34:1022, 1966.
24. Doyle, J. T., Dawber, T. R., Kannel, W. B., Kinch, S. H., and Kahn, H. A.: The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, N.Y., and Framingham, Mass., Study, *JAMA*, 190:886, 1964.
25. Seltzer, C. C.: An evaluation of the effect of smoking on coronary heart disease. I. Epidemiological evidence, *JAMA*, 203:127, 1968.
26. National Clearing House for Smoking and Health: The health consequences of smoking. A Public Health Service Review: 1967, Public Health Service Pub. No. 1696, Washington, D.C., Revised Jan. 1968.
27. Haskell, W. L., and Fox, S. M., III: The possible place of stress testing to discover, and physical activity to prevent, coronary heart disease, *Southern Med. J.*, 59:642, 1966.
28. Albrink, M. J., Meigs, J. W., and Granoff, M. A.: Weight gain and serum triglycerides in normal men, *New Eng. J. Med.*, 266:484, 1962.
29. Harlan, W. R., Jr., Graybiel, A., and Osborne, R. K.: Determinants of cardiovascular disease in a young population, *Amer. J. Cardiol.*, 15:1, 1965.
30. Albrink, M. J.: Triglycerides, lipoproteins, and coronary artery disease, *Arch. Intern. Med.*, 109:345, 1962.
31. Brown, D. F., Kinch, S. H., Doyle, J. T.: Serum triglycerides in health and in ischemic heart disease, *New Eng. J. Med.*, 273:947, 1965.
32. Carlson, L. A.: Serum lipids in men with myocardial infarction, *Acta Med. Scand.*, 167:399, 1960.
33. Gofman, J. W.: *Coronary Heart Disease*, Charles C Thomas, Springfield, Ill., 1959.
34. Lees, R. S., and Hatch, F. T.: Sharper separation of lipoprotein species by paper electrophoresis in albumin-containing buffer, *J. Lab. Clin. Med.*, 61:518, 1963.
35. Fredrickson, D. S., Levy, R. I., and Lees, R. S.: Fat transport in lipoproteins—an integrated approach to mechanisms and disorders, *New Eng. J. Med.*, 276:32, 94, 148, 215, 273, 1967.
36. Hatch, F. T., Moore, J. L., Lindgren, F. T., Jensen, L. C., Freeman, N. K., and Willis, R. D.: Semi-quantitative paper electrophoresis of serum lipoproteins (Abstract), *Circulation* 36: Suppl. II, 16, 1967.
37. Ostrander, L. D., Jr., Francis, T., Jr., Hayner, N. S., Kjelsberg, M. O., and Epstein, F. H.: The relationship of cardiovascular disease to hyperglycemia, *Ann. Intern. Med.*, 62:1188, 1965.
38. Walker, W. J., and Gregoratos, M. C.: Myocardial infarction in young men, *Amer. J. Cardiol.*, 19:339, 1967.
39. Stamler, J.: Cardiovascular diseases in the United States, *Amer. J. Cardiol.*, 10:319, Sept. 1962.
40. Paul, O., Lepper, M. H., Phelan, W. H., Dupertuis, G. W., MacMillan, A., McKean, H., and Park, H.: A longitudinal study of coronary heart disease, *Circulation*, 28:30, 1963.
41. Keys, A., Taylor, H. L., Blackburn, H., Brozek, J., Anderson, J. T., and Simonson, E.: Coronary heart disease among Minnesota business and professional men followed 15 years, *Circulation*, 28:381, 1963.
42. McDonough, J. R., Hames, C. G., Stulb, M. S., and Garrison, G. E.: Coronary heart disease among Negroes and Whites in Evans County, Ga., *J. Chron. Dis.*, 18:443, 1965.
43. Epstein, F. H., Ostrander, L. D., Jr., Johnson, B. C., Payne, M. W., Hayner, N. S., Keller, J. B., and Francis, T., Jr.: Epidemiological studies of cardiovascular disease in a total community—Tecomseh, Mich., *Ann. Intern. Med.*, 62:1170, 1965.
44. National Diet-Heart Study Final Report, *Circulation* 37: Suppl. I, 1968. Also available as American Heart Assoc. Monograph No. 18, American Heart Assoc., Inc., New York, N.Y.
45. Stamler, J., Berkson, D. M., Lindberg, H. A., Hall, Y., Miller, W., Mojonier, L., Levinson, M., Cohen, D. B., and Young, Q. D.: Coronary risk factors. Their impact, and their therapy in the prevention of coronary heart disease, *Med. Clinics N. Amer.*, 50:229, 1966.
46. Harlan, W. R., Jr., Oberman, A., Mitchell, R. E., and Graybiel, A.: Constitutional and environmental factors related to serum lipid and lipoprotein levels, *Ann. Intern. Med.*, 66:540, 1967.
47. Epstein, F. H.: Predicting coronary heart disease, *JAMA*, 201:795, 1967.
48. Siegel, D. G., and Krueger, D. E.: Consistency of incidence, survival, and prevalence data on myocardial infarction from various studies, *J. Chron. Dis.*, 20:603, 1967.
49. Truett, J., Cornfield, J., and Kannel, W.: A multivariate analysis of the risk of coronary heart disease in Framingham, *J. Chron. Dis.*, 20:511, 1967.
50. Mausner, J. S., Mausner, B., and Rial, W. Y.: The influence of a physician on the smoking of his patients, *Am. J. Public Health*, 58:46, 1968.
51. Galbraith, A., and Hatch, F. T.: A system of proportioned fat diets for clinical use, *Amer. J. Clin. Nutr.*, 16:480, 1965.
52. Reissell, P. K., Mandella, P. A., Poon-King, T. M. W., and Hatch, F. T.: Treatment of hypertriglyceridemia. I. Total caloric restriction followed by refeeding a low carbohydrate, high fat diet in the carbohydrate-induced type (8 cases). II. Low fat diet plus medium-chain triglycerides in the fat-induced type (2 cases), *Amer. J. Clin. Nutr.*, 19:84, 1966.
53. Eckstein, R. W.: Effect of exercise and coronary artery narrowing on coronary collateral circulation, *Circulation Res.*, 5:230, 1957.
54. Oliver, M. F.: Control of hyperlipidaemia, in *Modern Trends in Pharmacology and Therapeutics*, Fulton, W. F. M., Ed. Butterworths, London, 1967.
55. Coronary Drug Project: *JAMA*, 200:37, 1967.
56. Gofman, J. W., Young, W., and Tandy, R.: Ischemic heart disease, atherosclerosis, and longevity, *Circulation*, 34:679, 1966.
57. Gofman, J. W.: The quantitative nature of the relationship of coronary artery atherosclerosis and coronary heart disease risk, *Univ. Calif. Radiation Lab. Report No. 50270*, 1967, *Cardiology Digest*, in press, 1968.
58. Strong, J. P., Solberg, L. A., and Restrepo, C.: Atherosclerotic lesions in patients with coronary heart disease (Abstract), *Circulation*, 34:Suppl. III, 31, 1966.
59. Cornfield, J.: Joint dependence of risk of coronary heart disease on serum cholesterol and systolic blood pressure: a discriminant function analysis, *Fed. Proc.*, 21:No. 4, Part II, Suppl. 11, 58, 1962.
60. Frantz, I. D., Jr., and Ashman, P. L.: Design of dietary experiments for preventing myocardial infarction, *J. Amer. Diet. Assoc.*, 52:293, 1968.
61. Leren, P.: The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial, *Acta Med. Scand.*, Suppl. 466, 1966.
62. Christakis, G., Rinzler, S. H., Archer, M., Winslow, G., Jampel, S., Stephenson, J., Friedman, G., Fein, H., Draus, A., and James, G.: The Anti-Coronary Club. A dietary approach to the prevention of coronary heart disease—a seven-year report, *Amer. J. Pub. Health*, 56:299, 1966.
63. Bierenbaum, M. L., Green, D. P., Florin, A., Fleischman, A. I., and Caldwell, A. B.: Modified-fat dietary management of the young male with coronary disease, *JAMA*, 202:1119, 1967.
64. Turpeinen, O.: Diet and coronary events, *J. Amer. Diet. Assoc.*, 52:209, 1968.
65. Build and Blood Pressure Study, Society of Actuaries, Chicago, 1959.

66. Block, W. D., Jarrett, K. J., Jr., and Levine, J. B.: An improved automated determination of serum total cholesterol with a single color reagent, *Clin. Chem.*, 12:681, 1966.

67. Kessler, G., and Lederer, H.: *in* Technicon Symp. on Automation in Clinical Chemistry, Mediaid, Inc., New York, N.Y., 1965, p. 345

68. Noble, R. P., Hatch, F. T., Mazrimas, J. A., Lindgren, F. T., Jensen, L. C., and Adamson, G. L.: Comparison of lipoprotein analysis by agarose gel electrophoresis and ultracentrifugation (Abstract 106), *J. Amer. Oil Chem Soc.* 45:Feb 1968.

69. Technicon Autoanalyzer Methodology, Technicon Corp., Ardsley, N.Y., 1960.

70. Raab, W., and Gilman, L. B.: Report on study tour of German reconditioning centers. Insurance-sponsored, preventive, cardiac reconditioning centers in West Germany, *Amer. J. Cardiol.*, 13:670, 1964.

71. National Program to Conquer Heart Disease, Cancer and Stroke (Report to the President), Vol. I, Dec. 1964, p. 3.

72. Metropolitan Life Ins. Co., New York, N.Y.: Future gains in longevity after age 45, *Statistical Bulletin*, 48:8, March 1967.

ADDITIONAL RECENT REFERENCES

a. Hundley, J. M.: Heart disease: Recent trends in morbidity and mortality, *J. Amer. Diet. Assoc.*, 52:195, 1968.

b. Auerbach, O., Hammond, E. C., and Garfinkel, L.: Walls of arterioles and small arteries in relation to age and smoking, *New Eng. J. Med.*, 278:980, 1968.

c. Kaplinsky, E., Hood, W. B., Jr., McCarthy, B., McCombs, H. L., and Lown, B.: Effects of physical training in dogs with coronary artery ligation, *Circulation*, 37:556, 1968.

BRONCHOGENIC CANCER AND SMOKING

"I'm convinced that the most important factor in making a diagnosis of bronchogenic cancer is a history of smoking. I believe that in a man past 40 who has been a heavy cigarette smoker and who develops a thoracic complaint or discomfort, the burden of proof is upon the physician to disprove that he has bronchogenic carcinoma. . . . A man who has a lesion which is clinically cancer, but who is not a heavy smoker, either does not have cancer or he has an adenocarcinoma, which is rare. . . . Most patients have a cough. Many have thoracic discomfort. This is especially true of an individual who develops an atypical pneumonitis. It is true that a man past 40, who is a heavy smoker, can develop a viral pneumonitis, but I am convinced that the chances of the discomfort's really being due to cancer of the lung are much greater. . . .

"One way to improve the survival rate in lung cancer: Every individual—and this includes physicians as well as patients who are smokers—should have an x-ray of the chest at least every six months. And I believe that, if they live long enough and don't die of something else first, the heavy smokers will inevitably develop bronchogenic carcinoma. Is it going to do you any good to stop smoking now, because you've already smoked for 20 years? The American Cancer Society has studies to show that it does do your chances good to stop. They have shown that, in the individual who has been a heavy smoker and has stopped, the chances of developing a cancer of the lung are infinitely less than if he had continued to smoke. In the group of individuals who were heavy smokers and then stopped except for an occasional cigarette, the incidence of lung cancer was almost as high as if they had never stopped at all. In other words, if you are going to stop smoking, stop smoking completely."

—ALTON OCHSNER, M.D., New Orleans
Audio-Digest General Practice, Vol. 16, No. 12

MEDICAL STAFF CONFERENCE

Acute Leukemia

Current Concepts of Pathogenesis and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. WALTER BERGER:* The patient is a 23-year-old, unmarried, white female school teacher who was admitted to the medical service of the University of California San Francisco Medical Center for the first time on 27 December 1967 for evaluation of anemia. She said she had been in good health until, three months before admission, she noted the onset of progressive shortness of breath. After two months she began to have progressive fatigue also. Two episodes of spontaneous epistaxis occurred one week before her first admission to hospital. The day before this first admission she consulted her physician, who found a retinal hemorrhage and an hematocrit of 14 percent.

The patient gave no history of pain, fever, weight loss, melena, or of bleeding episodes or anemia occurring before the present illness. On physical examination at the time of entry she was found to have normal vital signs with blood pressure 120/60 mm of mercury, and pulse, respiration and temperature within normal limits. She was pale and appeared chronically ill but in no acute distress. The skin showed no signs of petechia, ecchymosis or purpura but bilateral fresh hemorrhages were evident in both fundi. She had generalized, shotty, non-tender lymphadenopathy. The lungs were normal to examination and the heart was normal

in size. A grade II/VI ejection murmur was heard at the left sternal border. No sternal tenderness was elicited. The liver appeared not to be enlarged but the spleen was palpated 2 centimeters below the left costal margin. Leukocytes numbered 16,000 per cu mm, with 36 percent polymorphonuclear cells, 6 percent band forms, 1 percent metamyelocytes, 19 percent lymphocytes and 38 percent immature forms, some of which contained Auer bodies. The hematocrit was 14 percent, reticulocytes 0.7 percent and platelets 250,000 per cu mm. Results of urinalysis were within normal limits, as were the serum creatinine and uric acid. On examination of bone marrow aspirate, sheets of myeloblasts were seen.

The patient was kept in hospital for five weeks while weekly courses of cytosine arabinoside ranging from 800 to 2,000 mgs were administered intravenously. There was only a slight improvement in bone marrow composition. Platelets decreased during the stay in hospital, falling as low as 12,000. The patient was discharged and was observed periodically in the out-patient clinic for two weeks while receiving weekly courses of 3 mg of vincristine intravenously. In the third week it was noted that the white blood cell count had risen to 42,000 with 80 percent blastocytes and she was readmitted to the medical service.

*Walter Berger, M.D., Resident in Medicine.

Physical examination at the time of reentry to hospital was essentially unchanged except for pronounced gingival hypertrophy and the presence of sternal tenderness. During the present stay in hospital the patient has had two four-day courses of daunomycin intravenously. The white blood cell count yesterday was 800 with 44 percent polymorphonuclear cells and 4 percent peripheral blastocytes. Problems during the current period in hospital have included fever to 39.6°C, the presence of hot, tender, erythematous nodules over the anterior tibial areas, and a draining perirectal abscess. Other medications during this hospitalization have included allopurinol, sodium bicarbonate, intravenous fluids and ampicillin. Her case is presented as one of acute myelogenous leukemia in an adult. There are no x-ray films to be shown.

DR. SMITH: * The patient is in isolation and is not here for presentation this morning. I believe she is a patient of Dr. Jackman.

Dr. Jackman has pointed out that this patient has appeared to be remarkably well-adjusted in her attitude toward her illness. She is fully aware of the diagnosis and its implications and has responded in a very mature way. We have asked Dr. Martin Cline to open the discussion with primary emphasis on the clinical manifestations and current approaches to treatment of acute leukemia. I think there are few areas in medicine which are more confusing to the general physician than that of chemotherapy of malignant hematological diseases. The proliferation of new agents and new mixtures of these agents in a desperate approach to treatment of these patients has added to these difficulties. Dr. Cline, why were these particular agents chosen? What is the rational approach to the treatment of such patients? Martin Cline has recently become Associate Director of the Cancer Research Institute here and is now in charge of the clinical unit of Medical Oncology. We are looking forward to having him elucidate this problem. I knew he had many talents, but I didn't know he had become a flower child as well (reference to a small flowering plant being placed on the x-ray projector).

DR. CLINE: † Last week Dr. Rudi Schmid, in discussing liver failure and ammonia toxicity, used the tomato plant as an example. I thought I would take this opportunity to demonstrate my own



Figure 1.—A periwinkle plant.

horticultural talents and brought with me a periwinkle plant. (Figure 1). This was not a random choice from my garden. From one variety of this ornamental plant, a potent anti-leukemic drug is extracted. Before considering the interesting history of this plant, however, I should like to consider several topics relevant to patients with acute leukemia. Specifically, I shall review current concepts of the clinical manifestations and treatment of acute leukemia and attempt to relate these to the emerging ideas about the proliferation and differentiation of malignant cells.

Clinical Manifestations

Let me consider first the clinical manifestations of acute leukemia in adults. The case history presented this morning was a remarkably good example of the cardinal manifestations of acute leukemia. The patient sought her physician's advice in the first place because of fatigue related to anemia. Later, hemorrhagic manifestations involving skin and retina became a problem and remained so over several months. In addition, her course in hospital has been punctuated by infections, of which the peri-rectal abscess has been the most persistent and difficult to treat. She has thus demonstrated several of the cardinal manifestations of patients with acute leukemia (Table 1).

TABLE 1.—Major Manifestations of Acute Leukemia	
I. Marrow and Organ Infiltrations	
A. red cell precursors . . .	anemia
B. platelet precursors . . .	thrombocytopenia, bleeding
C. granulocyte precursors .	granulocytopenia, infection
D. specific organ defects . .	liver, nervous system, bone, lung.
II. Metabolic derangements	
A. hypericemia	
B. hypercalcemia	
C. ? fever	

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.
†Martin J. Cline, M.D., Associate Professor of Medicine and Associate Director, Cancer Research Institute.

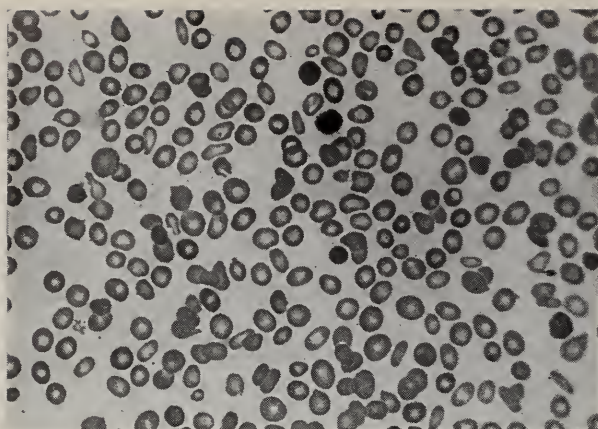


Figure 2.—Peripheral blood smear obtained when the patient was leukopenic. Aniso- and poikilocytosis and a nucleated red cell are apparent. Tear-drop forms are abundant.

These manifestations result primarily from a loss of normal marrow elements that is brought about either by physical crowding or, more likely, by competition for biochemical substrates.

Anemia results from both inadequate erythropoiesis and a shortened red cell life span. Morphological abnormalities with variation in the size and shape of erythrocytes and nucleated red cells in the peripheral blood (as in the present case) are common. (See Figure 2). Also common is granulocytopenia with increased susceptibility to infection and decreased platelets, with consequent bleeding tendency. As a rule of thumb, propensity to infection increases as the absolute neutrophil count falls below 600 per cu mm. We use this figure as a guide to determine whether isolation procedures are necessary for the patient. Similarly, we anticipate bleeding problems when the platelet count falls below about 50,000 per cu mm.

Almost every organ system shows microscopic evidence of leukemic infiltration. Clinically obvious malfunction is unusual, however, except in the case of the liver, nervous system (especially the central nervous system), lung and bone. Bone pain is frequent and sternal tenderness is often a good guide to leukemia in relapse. Rarely, osteolysis is associated with hypercalcemia.

Central nervous system involvement may be subtle, with minimal signs of objective neurologic disease. Consequently, persistent headache or "sinusitis" is sufficient indication for lumbar puncture. Pulmonary involvement is often a combination of direct pulmonary infiltration, bleeding and infection. These may be difficult to separate clinically. Although other organ systems are not usually involved clinically, in rare cases perforation of

the bowel or cardiac conduction defects may result directly from leukemic infiltration.

The hyperuricemia and increased urinary excretion of uric acid are easy to understand in view of the greatly increased nucleic acid turnover. Less easy to understand is the fever which often accompanies acute leukemia. In roughly one-half to two-thirds of patients a microbial origin can be demonstrated by culture, serology or responsiveness of fever to antibiotic therapy. In the remaining patients, no microbial cause can be demonstrated.

A clinical finding frequently noted in patients with acute monocytic or myelomonocytic leukemia is gingival hypertrophy and necrosis. This was a prominent feature early in our patient's illness. We had an extremely difficult time treating these painful, necrotic, malodorous gums.

The diagnosis of acute leukemia is simple when the white count is high. It is, of course, a morphologic diagnosis. There are relatively few conditions with which one can confuse acute leukemia with a high white count. However, about 40 percent of patients appear initially with a low white count. They are then said to have aleukemic leukemia. In these patients the diagnosis is established by bone marrow aspiration or biopsy. In the initial consideration of aleukemic leukemia the most frequent disease considered is aplastic anemia, which also presents with pancytopenia. The two conditions are easily separable by cellularity and cell content of the bone marrow. Interesting in this regard is that there has been an increasing number of reports of the association of aplastic anemia and acute leukemia. Acute leukemia may develop subsequently in patients who for several years have had aplastic anemia (usually related to drugs such as chloramphenicol and butazolidine).¹

Once the bone marrow is examined, the diagnosis of acute leukemia is usually obvious. Virtually the only diseases that can cause confusion are the occasional neuroblastomas of childhood with bone marrow invasion and malignant reticulo-endotheliosis such as Letterer-Siwe disease. In these disorders there may be primitive cells in the marrow which resemble cells of the hematologic series. Usually these can be easily distinguished from leukemic cells. The clinical manifestations are quite different in these disorders: involvement of the kidney in neuroblastoma, and prominent involvement of the bone, skin and lungs in Letterer-Siwe disease.

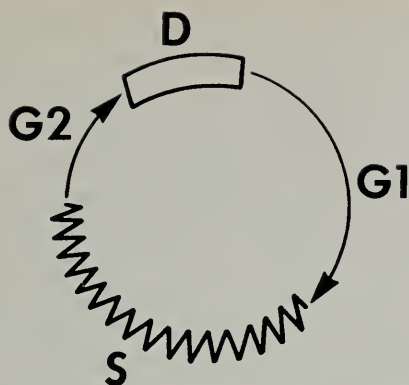


Chart 1.—The life cycle of a dividing cell. D is the period of mitosis or cell division. G1 is the phase before DNA synthesis. S is the phase of DNA synthesis. G2 is the pre-mitotic period.

I shall not dwell on the morphologic characteristics of the leukemic cell. For physicians who are not hematologists, the chief feature of leukemic bone marrow is that of infiltration with reduction in the fat spaces. There is a deadly uniformity of the slide. The cells are crowded and all look approximately the same in size and staining qualities because they are all more or less at the same stage of development. A good hint in defining the morphologic type of leukemia is to identify a primitive cell by the company it keeps. If there are cells with granules or Auer rods, one is usually concerned with myelocytic or myelomonocytic leukemia.

The Cell Cycle and Differentiation

I would like to consider briefly the relationship of these manifestations of acute leukemia and of its treatment to cellular replication and to proliferation. A cell that is capable of proliferation—let us call it a stem cell—is faced with two choices: It can make another stem cell, which is capable of further proliferation, or it can make a differentiated cell which is no longer capable of proliferation and which may pass on through a series of further differentiations until it reaches some end cell. The latter sequence might be envisioned for the first identifiable primitive cell of the erythrocytic series which goes on and makes the mature red cell. The myeloblast has the option of dividing to furnish additional blast cells or of differentiating toward the mature neutrophil. What determines which of these paths a cell pursues? I think it is fair to say that we do not know the answer to this intriguing question. There are only faint glimmers. In certain circumstances differentiation of cells is probably influenced by extracellularly derived hormones. For example, erythropoietin en-

courages differentiation of primitive hemopoietic cells toward the red cell series. We do not know if similar humors are responsible for leukocyte differentiation. The defect in cellular differentiation in acute leukemia is unknown. Is it related to the chromosomal anomalies so frequently observed in these cells? Of unknown significance is the observation that only a fraction and sometimes a small fraction (10 percent or 20 percent) of the blast cell population is actively synthesizing DNA and dividing. The rest are dormant. In acute lymphoblastic leukemia, the cells with a high proliferative rate are usually the large rather than the small blast cells.

An important concept regarding the proliferation of acute leukemic cells is derived from animal model systems. There appears to be little or no host defense mechanism against the leukemic cell. A single leukemic cell inoculated into an animal will produce fatal leukemia.^{2,3} This observation is central to the concept that every single leukemia cell must be eradicated in order to cure the disease. How very difficult this task is becomes obvious when one realizes that there are no clinically detectable signs of the disease until the body burden of leukemic cells reaches approximately 10 billion to 1,000 billion. A drug which is 99.999 percent effective would still leave 10^5 to 10^7 leukemic cells, which would be undetectable until they again proliferated and reached a critical mass.

To appreciate how antileukemic drugs work, it may help to consider the life cycle of a proliferating cell such as a myeloblast.

A convenient place to start in the life cycle is with the initiation of cell division, mitosis. This occupies a discrete phase of the life cycle which we will designate as D for division (Chart 1). After the cell has completed its replication it passes on to another phase, which for a long time had been considered a relatively quiescent phase. Biologists have termed cells in this phase "G-1." From this quiescent phase it then begins one of DNA synthesis, which the cell biologists have chosen to call S. After completion of DNA synthesis, the cell again goes into what was thought to be a resting phase before initiation of mitosis. This phase of apparent rest is called G-2.

Certain interesting features of this cycle have emerged in the past few years. Traditionally the morphologists have concentrated on the rather dramatic events of mitosis and cell division with its formation of the spindle, separation of the

chromosomes and so forth. It is only recently that the other aspects of the cell proliferation cycle have received any attention at all. One feature now clearly emerges. In most dividing cells the periods for DNA synthesis (S), for the G-2 phase and for division (D), are relatively fixed in time. They are nearly constant. Variation in the length of the cell cycle generally occurs in the G-1 phase. When cells come to rest after stopping proliferation, they stop in the G-1 phase, not in the S or the G-2 or the division phase. For example, after partial hepatectomy and liver proliferation the liver cells stop dividing and end in the G-1 phase.

This phase is not at all the inactive period it was once thought to be. There is very active RNA and protein synthesis during this period. The duration of the G-1 phase seems to be related in some way to the proliferative activity of the tissues. When the proliferative activity is high, the G-1 phase is short. When the proliferative activity is low, the G-1 phase tends to be long. For example, if you carry out partial hepatectomy in an animal, there is a considerable lag before DNA synthesis starts. Similarly the lymphocyte (once thought to be a non-dividing cell) arrested for a long time in the G-1 phase when it is exposed to an antigenic stimulus or to phytohemagglutinin, goes through a prolonged G-1 phase of several days before DNA synthesis actually begins. In very rapidly proliferating protozoa or the very early embryo, the G-1 phase may be essentially obscured. It is only as tissues develop and become differentiated that the G-1 phase becomes manifest. This phenomenon may be a characteristic aspect of cellular differentiation.

What instructs a cell to leave G-1 and begin the DNA synthesis phase? This is really not clear at all in mammalian cells but some very exciting information is beginning to come from studies on bacterial replication in which there is evidence that particular proteins or polypeptides may be necessary for the initiation of the synthetic phase. The control mechanisms in higher cells seem to require interaction between the nucleus and the cytoplasm of the replicating cell. The evidence for this runs something as follows: If one takes a nucleus from an amoeba which is in the G-2 phase after it has completed its DNA synthesis and transplants this nucleus into the cytoplasm of an S phase amoeba, then the nucleus will resume DNA synthesis. It seems to be getting instruction from the cytoplasm.

Once the S phase begins, several things start to

happen. The enzymes necessary for DNA synthesis, including the basic ones involved in purine and pyrimidine biosynthesis, turn on and increase in specific activity. It is at this time that cells will take up tritiated thymidine, used as an experimental marker. Once DNA synthesis is complete, there is a G-2 phase which is, as I say, relatively fixed in length in most cells. It was thought to be a quiescent phase but now it is quite clear that there is a requirement for RNA and protein synthesis before one can construct the mitotic apparatus and go through division. It may be at this point in the cell cycle that certain mitotic inhibitors such as colchicine and vincristine exert their effect. These considerations of cell cycle are critical in the use of chemotherapeutic agents. As a generalization, replicating cells are sensitive to attack by the commonly used antimetabolites only during the S phase.^{4,5} It is obvious, then, that these agents will be relatively ineffective with slowly turning over cell populations with a high percentage of dormant cells. On the other hand, alkylating agents and drugs interacting primarily with macromolecular DNA (for example, daunomycin) seem to act largely independently of the stage of the cell replication cycle.

Treatment

Let me now consider treatment. What are the objectives of therapy in the patient with acute leukemia? The objective is induction of a complete hematologic response; that is, a return of the blood and bone marrow to the normal conditions (as far as one can define this morphologically). Most physicians would agree that the objective of treatment is an improvement in the feeling of well-being of the patient and a prolongation of life. In acute lymphoblastic anemia there is a good correlation between survival and the induction of the first hematologic remission. This is less clear in acute myeloblastic leukemia. Important to the concept of the objectives of therapy are the observations that leukemic cells can proliferate in certain privileged sites outside the attack of the usual drugs. These privileged sites result from the fact that most of the drugs we use do not cross the blood-brain barrier. Thus, while one is effectively controlling the disease in the blood, the bone marrow and parenchymal organs, the cells are proliferating with impunity within the central nervous system. This site requires a separate attack.

I should like to consider two aspects of therapy

TABLE 2.—*Supportive Therapy for Patients with Leukemia*

Red cells
Platelets
Antibiotics
Sterile precautions
Uricosuric agents or
xanthine oxidase inhibitors
White cells

—supportive and specific. In the past I tended to describe supportive therapy rather briefly, considering it fairly obvious and well known. However, since it has become possible to greatly prolong the lives of patients with these diseases, the critical limitations have come in supportive therapy and not in ablative chemotherapy. I have indicated that bleeding and infection are the two most important clinical problems leading to death. It is obvious that if one could replace white cells and platelets with complete freedom, he could sustain leukemic patients for a considerable length of time. It is already possible to replace platelets, and as you will see it may be equally possible in the near future to replace white cells.

Table 2 lists the principal requirements of supportive care. Obviously red cells are needed for anemic patients, and platelets for severely thrombocytopenic patients. The points I would make about platelets are these: When platelets are given, they must be given in adequate numbers—a minimum of 8 units for an adult. One does not wait until the patient is actively bleeding before giving the platelets. By then it is generally too late. Therefore the guideline is a platelet count under 30,000 per cu mm and peripheral manifestations of skin or nose bleeding.

Infusion of white cells can be quite effective in patients who are granulocytopenic and have an infection. This was first demonstrated by the studies at the National Cancer Institute in which leukocytes from patients with chronic myelocytic leukemia were given to children with acute leukemia who had unresponsive infections (often with pseudomonas). Not infrequently there was a dramatic clearing of these infections. Detailed studies demonstrated that these donor white cells persisted for reasonable periods, often several months. Evidence of persistence was based on marrow karyotypes, including analysis for the Philadelphia chromosome and female karyotypes in the recipient.

Antibiotics as supportive measures are obvious, as are sterile precautions. Now that we have an

TABLE 3.—*Chemotherapeutic Agents Used in Treatment of Leukemia*

ANTIMETABOLITES
purine analogues : 6 mercaptopurine
pyrimidine analogues : cytosine arabinoside
folic acid antagonists : methotrexate
Alkylating agents : cyclophosphamide
Irradiation
Corticosteroids : prednisone
Plant alkaloids : vincristine
Antibiotics : daunomycin
Enzyme antagonists : L-asparaginase

effective xanthine oxidase inhibitor (allopurinol) with low toxicity, uric acid should no longer be a problem. I would stress that prevention of the renal complications of hyperuricemia is much easier than treatment of the established disease.

Specific Therapy

What about specific therapy? I agree with Dr. Smith that this is an area confusing to most physicians not regularly involved in the care of cancer patients. To simplify matters I have grouped the agents according to mode of action (Table 3), and have listed the agents most commonly used in the acute leukemias. The first three drugs listed are antimetabolites — purine and pyrimidine analogues and the folic acid antagonists. We know quite well how these agents act and I shall not consider the details of their mechanism of action. All these compounds appear to work during the S phase of the cell cycle. It is worth mentioning that a new class of pyrimidine analogues has appeared in which the chemical modification is in the sugar moiety rather than the nitrogenous base. This drug (cytosine arabinoside) now has an important place in therapy. The second class of therapeutic agents we should consider are the alkylators and irradiation—alkylating agents such as cyclophosphamide for systemic therapy and irradiation for local problems. They seem to work by roughly similar mechanisms: Interaction with the DNA molecule producing breaks in or cross linking of the DNA strands. (Their cytotoxic action does not appear to be specific for a particular phase of the cell cycle.)

A third class of agents, corticosteroids, are important drugs for acute leukemia. Although these compounds have been available a long time, the precise mechanism of action is unknown. A relatively new class of compounds is that of the plant alkaloids. The most important of these is vincristine. This brings us back to the plant I brought in this morning (Figure 1). It is a variety of the

periwinkle plant. An alkaloid, vincristine, is extracted from the Madagascar periwinkle. The plant has a rather interesting history. It has been used by the natives of the island of Jamaica in the treatment of diabetes, presumably as a hypoglycemic agent. Consequently one of the large botanical drug houses in this country put an extract of the plant through its screening program for hypoglycemic agents. All the treated mice died, probably as a result of infection associated with granulocytopenia. The pharmacologists then put the extract through their chemotherapy screening program and we now have the Vinca alkaloids as chemotherapeutic drugs. These compounds are interesting in that they are an entirely new class of agents used in the treatment of acute leukemia. They produce metaphase arrest and inhibit RNA and protein synthesis. They are cell cycle specific.

Another new agent that has very recently appeared and is very interesting because it provides a new tool and a new method of attack is daunomycin, an antibiotic extracted from one of the streptomyces. Because of its color it is also called rubidomycin. This compound seems to act very much as actinomycin does, in that it interacts with DNA strands, specifically with the guanine residues. As a result, it blocks DNA and RNA synthesis. Whereas actinomycin is of relatively little help in leukemia, daunomycin is quite effective. It appears to act at all phases of the cell cycle.

A very exciting new compound is L-asparaginase. This chemotherapeutic agent is unique and it has a rather interesting history. A cell biologist observed that his tissue cultures of lymphoma cells died when guinea pig serum was added to the medium. Subsequent analysis over several years revealed that the active factor in guinea pig serum was L-asparaginase, an enzyme which deaminates the amino acid L-asparagine. This amino acid is not an essential growth factor for normal tissues but is essential for certain malignant tissues, particularly the lymphomas and leukemias. It is essential in the sense that these tumors cannot synthesize this amino acid but must obtain it from extra-cellular sources. Hence if an enzyme capable of destroying the amino acid is added to the external medium, then the only source of supply to the malignant cells is cut off. The first tests of this compound were performed in Boxer dogs, for a type of lymphoma frequently develops in them.

The tests were eminently successful and the compound is now being studied in man.

As you might expect, all of these chemotherapeutic agents are similar in their toxicities to rapidly proliferating cells. The rapidly proliferating cells of the body are those of the bone marrow, the gastrointestinal tract and the hair follicles. Therefore the unwanted effects one anticipates are gastrointestinal disturbance, baldness, and marrow suppression. In addition, each of the agents seems to have its own peculiar toxicity. Cytosine arabinoside seems to be primarily G.I. toxic. 6-Mercaptopurine can produce jaundice of a peculiar type. Methotrexate seems to be especially toxic to the cells of the buccal mucosa and commonly produces ulcerations of the mucosa. The metabolic products of cyclophosphamide appear in the urine. They are irritating to the bladder and can produce a severe hemorrhagic cystitis. Vincristine among the Vinca alkaloids is highly neurotoxic, producing both sensory and motor neuropathic changes. This neuropathic effect constitutes the main limitation to the use of this drug. Daunomycin is primarily marrow toxic, but in about one case in ten produces an unusual cardiomyopathic change. L-asparaginase brings about high fevers.

Faced with this list of agents, how does the physician decide which one or which combination to use? In Table 4, I have listed what I would consider "traditional" or conservative therapy of the various kinds of acute leukemia. Acute lymphoblastic leukemia is the most frequent acute leukemia of childhood. Acute leukemia of adults is usually myeloblastic or myelo-monoblastic. Considering first acute lymphoblastic leukemia, the best *initial* treatment is a combination of vincristine and prednisone for four to six weeks. With this regimen, one can induce a remission well over 80 percent of the time. Once remission is induced, the steroids are reduced and the vincristine is discontinued. Administration of 6-mercaptopurine or methotrexate alone is then begun or the drugs are given in alternate cycles of four to six weeks. Almost invariably the disease relapses. This first relapse is usually treated with prednisone or with prednisone and vincristine. If a second remission is achieved maintenance therapy is reinstituted. If a second remission is not achieved with prednisone and vincristine, a number of less effective agents are available (Table 4). These other agents are considered for all subsequent relapses.

I wish to point out that after the first relapse,

TABLE 4.—Therapy of Acute Leukemia

ACUTE LYMPHOBLASTIC LEUKEMIA

1. prednisone and vincristine: 1st remission induction
2. 6-mercaptopurine/methotrexate: maintenance
3. prednisone and vincristine: 2nd remission induction
4. 6-mercaptopurine/methotrexate: maintenance
5. cyclophosphamide
cytosine arabinoside } 2nd or 3rd remission
daunomycin } induction
combination therapy }

ACUTE MYELOMONOCYTIC LEUKEMIA

- | | |
|--|------------------------------|
| cytosine arabinoside | } 1st remission
induction |
| vinc. + meth. + pred. + 6-MP | |
| cytosine arabinoside + purine analogue | |
| ? daunomycin | |

the choice of agents is imprecise and a matter of clinical judgment. Our laboratory has been engaged in trying to develop test systems which will make the choice of drug more precise. I shall consider these tests in a moment.

Let us briefly consider the treatment of acute myelomonocytic leukemia. To speak of "traditional therapy" in this disorder is virtually meaningless since treatment with agents in existence more than five years ago produced remission in somewhat under 8 percent of patients. Therefore we are still exploring the optimal use of the new agents in this highly malignant disorder. As a rule, therapy is less successful and survival is shorter in this disorder than in acute lymphoblastic leukemia of childhood. However, there is some reason for optimism. Therapy of acute leukemia of adults is outlined in Table 4. With the new agents listed in this table we can now anticipate remission in between a 20 percent and 35 percent of cases. You will recall that the patient under discussion today was treated sequentially with several of these agents.

I would stress two points. First, the optimal therapeutic program in these diseases remains to be determined. Secondly, the supporting care is enormously costly and requires a dedicated team. For these reasons I would usually advocate referral of the patient with acute leukemia to a specialized treatment center interested in this disorder.

I would like to describe briefly our attempts to develop a more rational method of selecting chemotherapeutic agents. For the past three years we have been interested in developing a test system for predicting which of several alternative drugs was going to be effective in the treatment of a given patient. This interest arose from some studies of the effect of vincristine on leukemic cells *in vitro*. Vincristine was thought primarily to be an inhibitor of mitosis, causing metaphase arrest of

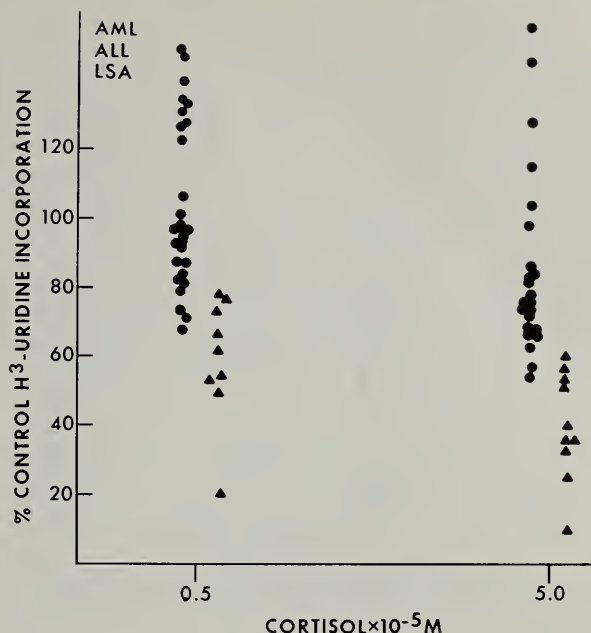


Chart 2.—Correlation between the *in vitro* effect of cortisol on leukocytes of patients with acute myelocytic leukemia (AML), acute lymphoblastic leukemia (ALL) and lymphosarcoma (LSA), and the clinical response to glucocorticoids. Cortisol was added *in vitro* at concentrations of 0.5 or 5 $\times 10^{-5}$ M and the incorporation of H³-uridine compared to that in control cultures. Patients designated by ● failed to respond to steroids *in vivo*. Patients designated by ▲ made a good clinical response to steroids.⁸

dividing cells. We found that vincristine was in addition an exceedingly potent inhibitor of RNA and protein synthesis in leukemic cells.⁶ This latter effect is probably the major basis of its anti-leukemic action. Since vincristine inhibits RNA synthesis *in vitro*, we asked if one could use this property to predict which leukemic cell populations were going to respond *in vivo*. After a considerable amount of work, we developed a rather simplified test system: Leukemic cells are cultured *in vitro*, drug is added to the culture and the incorporation of radioactive uridine is measured over a given period of time. By quantitating the extent of inhibition of RNA synthesis, one obtains a measure of the effectiveness of a given drug *in vitro*. The major question to be asked has to do with the correlation between the *in vitro* effect of the drug and its clinical effectiveness in a patient with leukemia. In fact, there does seem to be a good correlation between the test tube results and the clinical responsiveness to corticosteroids and vincristine (Charts 2, 3, and 4 and References 7, 8). We are still working on test systems for cytosine arabinoside and daunomycin.

Time will not permit showing where the studies on the white cells of the patient we are discussing

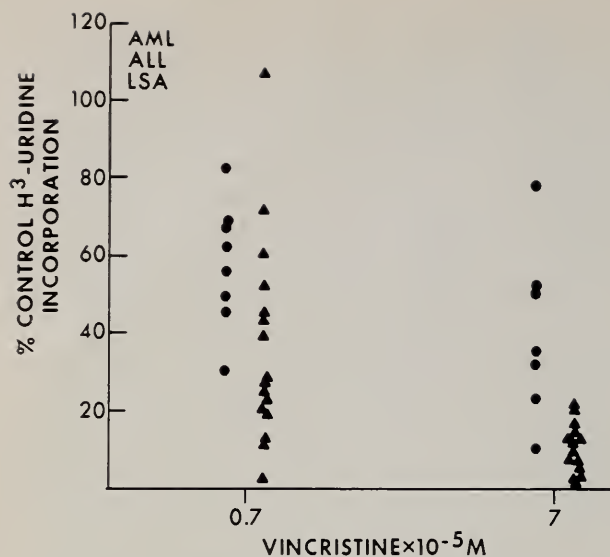


Chart 3.—Correlation between effects of vincristine *in vitro* and *in vivo*. Same conditions as in Chart 4.

this morning fell on the curves of drug responsiveness. Suffice it to say they were only slightly sensitive to cytosine arabinoside and vincristine, but quite sensitive to daunomycin.

Areas for Future Advances

In the last minutes remaining I would like to attempt to predict where leukemia research is going

in the next few years. Obviously we are just beginning to develop a better understanding of the controlling factors in cell replication and differentiation. The relevance of such information to acute leukemia is obvious. The concept of exogenous immunologic defense mechanisms (for example, sero-therapy) is emerging and may be exploitable. Such therapy may circumvent the requirement of reducing the number of leukemic cells to zero by chemotherapy before a cure can be achieved.

A critical problem in achieving cure is deciding when the leukemic cells have been eliminated. It is often not difficult to wipe out leukemic cells. There are usually enough drugs and enough tools on hand to do this. The problem is to decide how long and how vigorously one has to pursue therapy—always with the limitation that normal tissues must not be damaged irreparably. Therefore we need some sort of markers of persistence of leukemic cells when they are no longer visible morphologically. A marker such as serum lysozyme elevation in acute monocytic leukemia may serve this function.

Obviously advances are going to be made in therapy. We now have new drugs with new modes of action. Exciting drugs such as daunomycin and L-asparaginase open up new methods of attack on malignant proliferating cells. The use of drugs in

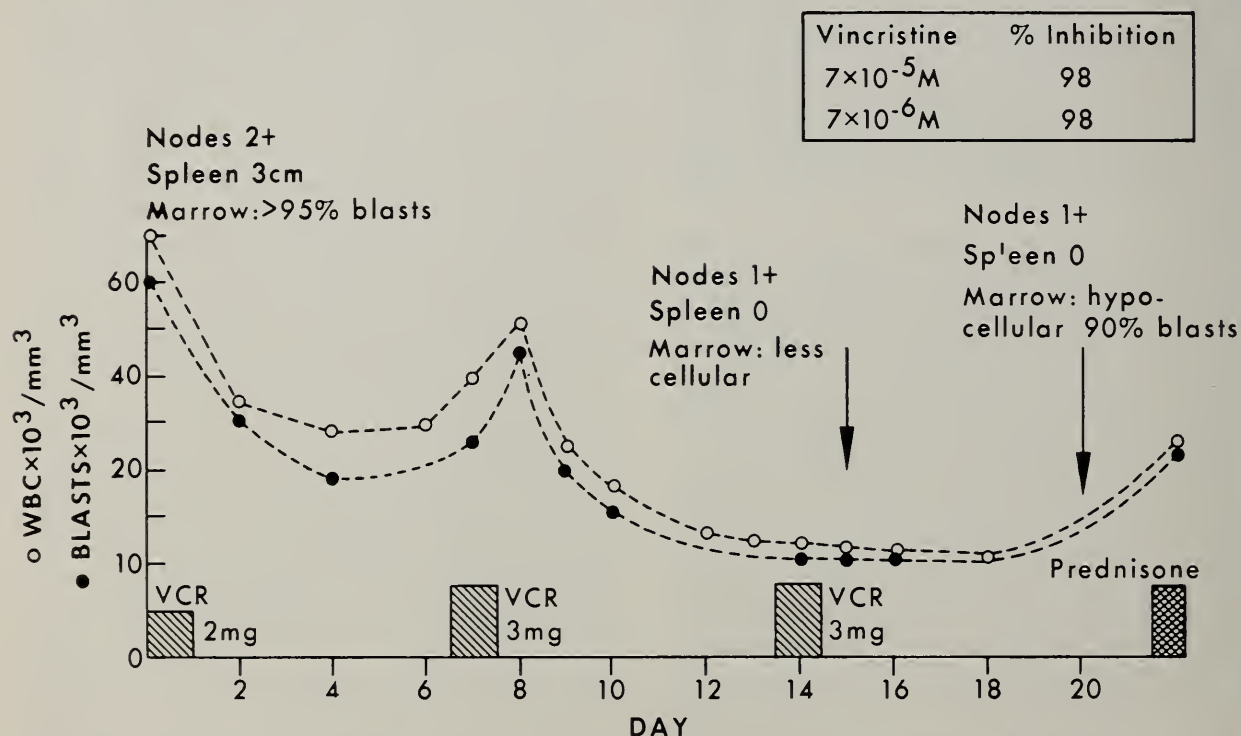


Chart 4.—Clinical effectiveness of vincristine in a 14-year-old boy with acute lymphoblastic leukemia. By *in vitro* testing of isolated leukocytes, his disease was predicted to be responsive to vincristine.

combination is already being exploited and investigations along this line will continue. A critical issue in the use of new drugs will be the timing of their administration to coincide with the sensitive period in the cell cycle. Techniques for artificially cycling malignant cells may be developed. Perhaps the most critical area in therapy is that of supportive therapy. Platelets are already available. The question is whether white cells can be made available. I think they can. For example, the Irwin Memorial Blood Bank in San Francisco processes roughly three to four hundred units of blood a day. From each of those units one could obtain the buffy coats. Combined they would easily support two or three patients with aplastic anemia or acute leukemia during critical periods of infection. Solving this particular problem, then, becomes a matter of logistics and the financing. Once white cells are available, the problem of infection is potentially solvable.

What has actually been accomplished in leukemia therapy in the last few years? One has only to look at the history of this disease to become aware of the remarkable advances. Before the chemotherapy era, life expectancy in the acute leukemias was between five and twenty weeks. With the advent of methotrexate and 6-mercaptopurine, this rose to approximately 12 months. Now life expectancy is approaching two years in the case of acute lymphoblastic leukemia. Most large institutions have a number of patients who have survived two, three and occasionally four years. The concept has emerged that this malignant disease, like some of the malignant tumors, is potentially curable. If we can support a patient through the period

of drug induced toxicity and aplasia, we may eradicate the malignant cells and cure him. I should not be surprised if five or ten years hence we can look back on this disease and classify it among the curable disorders.

DR. SMITH: Are there any comments from the audience?

DR. SALMON: * I might comment that in the exciting new field of enzyme therapy of leukemia, predictive *in vitro* test systems have already proved to be quite valuable.

DR. SMITH: Will the same background information allow one to approach leukemia by developing structural analogues of asparagine itself? This should be a logical extension of current research.

DR. CLINE: That is the next logical extension and such studies are already in progress.

*Sidney Salmon, M.D., Assistant Professor of Medicine.

REFERENCES

1. Cohen, T., and Greger, W. P.: Acute myeloid leukemia following seven years of aplastic anemia induced by chloramphenicol, *Am. J. Med.*, 43:762-769, 1967.
2. Furth, J., and Kahn, M. C.: Transmission of leukemia of mice with a single cell, *Am. J. Cancer*, 31:276, 1937.
3. Skipper, H. E., Schnabel, F. M., Jr., and Wilcox, W. S.: Experimental evaluation of potential anti-cancer agents—XIV. Further study of certain basic concepts underlying chemotherapy of leukemia, *Cancer Chemother. Rep.*, 45:5-28, 1965.
4. Rall, D. P.: Selective aspects of chemotherapy in acute leukemia and Burkitt's tumor, *Cancer*, 21:575-579, 1968.
5. Skipper, H. E.: Biochemical, biological, pharmacologic, toxicologic, kinetic and clinical (subhuman and human) relationships, *Cancer*, 21:600-610, 1968.
6. Cline, M. J.: Effect of vincristine on synthesis of ribonucleic acid and protein in leukemic leukocytes, *Brit. J. Haemat.*, 14:21, 1968.
7. Cline, M. J.: Prediction of *in vivo* cytotoxicity of chemotherapeutic agents by their effect on malignant leukocytes *in vitro*, *Blood*, 30:176, 1967.
8. Cline, M. J., and Rosenbaum, E.: Prediction of *in vivo* cytotoxicity of chemotherapeutic agents by their *in vitro* effect in leukocytes from patients with acute leukemia, *Can. Res.*, in press 1968.

A SIGN TO RULE OUT PHEOCHROMOCYTOMA

"I asked an endocrinologist to tell me if this patient had a pheochromocytoma; and he stared at the back of the patient's hands and said: 'The veins are dilated, so the patient does not have a pheochromocytoma—though we'll go ahead and do the catecholamines in the urine anyway.' Well, he didn't have any; and this made quite an impression on me because, since then, I've never seen a patient with pheochromocytoma who had dilated, distended veins like most of us have in a warm room."

—JAMES D. HARDY, M.D., Jackson, Miss.
Audio-Digest *Anesthesiology*, Vol. 10, No. 11

CASE REPORTS

Pica in Adults

WALLACE M. MITCHELL, M.D., *Los Angeles*

PICA, THE TERM referring to the habit of eating clay, plaster, ashes or the like, has been observed in many people in all parts of the world from ancient times. There have been frequent reports of pica in children in the modern medical literature but the occurrence of pica in adults other than pregnant women has only rarely been reported recently. A case of pica in a woman who was not pregnant is presented here and the available literature reviewed.

Report of a Case

The patient was a 26-year-old Caucasian woman who said that she had been eating clay daily for two years and for five years before that had had a craving for it. She had eaten it in the form of pottery (cups, figurines) or brick. The aroma of wet cement, the patient said, was very pleasant to her. She said that she ate clay because of the taste but thought that she might have some nutritional lack to give rise to the peculiar craving. She knew of no one else who ate clay. Her husband thought it was a strange habit but made no strong objections.

The patient was born in Texas of Latin American parents. She had two brothers and one sister. The father and the sister had asthma. There was

no family history of pica. The patient felt that she had a normal childhood and adolescence. She had not done well in school and had quit at grade 11 and begun to work, first in a fruit-packing establishment, later as an electronic assembler. Before marriage she had had one child. Her marriage had been marked by considerable conflict. She had been pregnant twice since marriage, each pregnancy accompanied by nausea and vomiting, the most recent by hyperemesis gravidarum. There was a long history of unexplained fatigue, "rheumatism," constipation, feeling faint in crowds, transient nervousness and depression.

No abnormalities were noted on physical examination. The patient was alert, oriented, tense but pleasant and cooperative. Her talk was relevant but she was not generous in giving personal information. There was no bizarre ideation and her affect was appropriate. Her mood seemed one of mild depression. She appeared to be of average intelligence.

Laboratory studies revealed hypochromic anemia, (hemoglobin 11.0 gm per 100 ml of blood, hematocrit 33 percent), a low serum iron (40 mcg per 100 ml), high iron-binding capacity (430 mcg per 100 ml) and low percent of saturation (9 percent). Results of all other laboratory studies were within normal limits.

A personality factor questionnaire¹ revealed a very high general neuroticism level with other indications of high levels of anxiety, a proclivity toward psychosomatic symptoms and a tendency to be suspicious, inhibited, moody and shy.

In summary, the patient was believed to have a schizoid personality with a psychoneurotic reaction manifested by anxiety and other defenses such as her transient somatic complaints, hyperemesis during pregnancy, and pica. An incidental finding was mild iron deficiency anemia due to inadequate dietary iron.

The author is Instructor, University of California, Irvine, California College of Medicine; Attending Physician, Psychiatry, Los Angeles County General Hospital; and Head Physician, Internal Medicine, Los Angeles County General Hospital.

Submitted 26 January 1968.

Reprint requests to: University of California, California College of Medicine, 1721 Griffin Avenue, Los Angeles 90031.

Review of the Literature

Ancient Greek writers commented on the occurrence of pica in pregnant women. Later, a number of European writers from the 15th to 18th centuries offered theses on the causes of pica in men, women and children, implicating such diverse etiologic factors as heredity, obstruction of the viscera, suppression of menses, nutritional deficiency, mental conditions, and mysterious humours. Modern anthropologists and explorers² have noted clay eating to occur in certain groups of people in Asia, Africa, Europe and North and South America. In sections of Afghanistan,³ clay was prepared in edible form and sold in shops and bazaars. In certain sections of Northern Europe⁴ clay was prepared in the form of loaves, cups, human figures and the like and then baked and sold in the streets or markets, the demand springing from belief at that time in a number of beneficial effects—that eating these products cured syphilis, assured fine progeny or remedied constipation. In the southern United States and West Indies, clay eating was a matter of concern to colonial physicians and plantation owners.⁵ Most of those who wrote of the phenomenon at the time associated pica with anemia and a diet inadequate in quality or quantity. The usually recommended therapy stressed the use of iron preparations, a plentiful and varied diet and healthful living conditions. In the medical literature throughout the latter part of the 19th and 20th centuries, sporadic reports of pica in adults implicated nutritional or psychological factors or parasitic infestation.

Cooper,⁶ in an extensive review, surveyed the historical literature as well as reports from the field of veterinary medicine and anthropology concerning pica. Pica in adults is mentioned in recent papers by observers in Turkey⁷ and the United States.^{8,9,10,11} These investigators viewed pica in the adult as an acquired psychological habit rather than a symptom of nutritional deficiency. Among clay eaters of the southern United States, clay is taken most often because of a "craving," less often for specific symptom relief such as headache, nervousness, dizziness, vomiting, disgust, or during pregnancy to bear a healthy infant or prevent some complication.

To a certain extent, the clay eating is promoted or sanctioned by cultural influences and superstitions but in many instances the clay eater maintains that it was on her own initiative that she

began the habit. As in the case presented herein, often members of the family of the clay eaters, while not approving of the habit, feel it better for the person to eat clay than not to satisfy a craving for it.

Discussion

The cause of pica is obscure. Laboratory animals with experimentally produced deficiencies have been observed unerringly to compensate for such deficiencies by consuming unusual amounts of the required nutritional elements if they are made available.¹² It has been shown also that the taste threshold varies with internal needs.¹³ That the modern human infant is capable of selecting a diet which provides well for his nutritional status has been demonstrated.¹⁴ Although it has been frequently suggested that pica is an attempt to remedy a nutritional lack, the treatment of pica with nutritional elements yields conflicting results. Some investigators have reported that iron is curative in children,¹⁵ others finding placebos as effective.⁸ Most modern observers have expressed belief that although poor nutrition may be associated with pica in adults, it is not causal; they believe that the etiology involves numerous environmental, cultural and psychological factors. While pica appears to occur in relatively high incidence in groups of people who have too little food, or in groups with some superstitious belief in a therapeutic action of the ingested substance, it also occurs sporadically. It has been noted in deteriorated schizophrenic persons¹⁶ and in the mentally retarded¹⁷; and in children it may be part of a more generalized behavior disorder.¹⁸ In the majority of reported cases of pica in the adult, psychiatric appraisal has been cursory or not mentioned at all, but most patients have apparently not been grossly psychotic. Sporadic cases of pica in adults probably represent in most instances a manifestation of a severely neurotic personality, as apparently it was in the present case.

Food has emotional rather than intellectual value to the average person. Knowledge of the emotional value of food is much older than the knowledge of its nutritional value. One of the primordial urges is the urge to eat, a necessity to preserve life. In ancient times, food was obtained solely to satisfy this biological urge. In modern Western civilization, where food supply is no problem, food is meaningful as a symbol in many

social interactions, in cultural identification, as a badge of prestige and social position; and it is endowed with many psychological and emotional overlays.^{19,20} It is visualized by most persons in these contexts, rather than as a source of nutrients for growth and metabolism. These emotional overtones are probably initiated very early in life when the infant associates food and the feeding process with love, pleasure, protection and comfort. Later in life, each person develops his own galaxy of food — associated emotional tones, many of them unconscious, wrought by his own individual experiences and the hope, fear and superstition of his culture. In extreme forms, food aversions or cravings, including pica, occur.

Summary

Pica, a symptom usually associated with children, pregnant women or special cultural groups, is occasionally observed in an adult who is not pregnant. Since ancient times many explanations have been offered as the cause of this peculiar habit, but there is general agreement today that pica in adults is psychogenic, as it appeared to be in the case here reported.

REFERENCES

1. Cottell, R. B., and Eber, H. W.: Handbook for the Sixteen Personality Factor Questionnaire, Institute for Personality and Ability Testing, Champaign, Ill., 1957.
2. Lauffer, B.: Field Museum of Natural History, Publication 280, Anthropological Series, XVIII:2, 1930.
3. Hooper, D., and Mann, H. H.: Earth eating and the earth eating habit in India, Mem. of the Asiatic Soc. of Bengal, 1:249, 1906.
4. Lasch, R.: Ueber geophagie. Mitt. Anthropol. Gesellsch., Wien, 28:214, 1898.
5. Craigin, F. W.: Observations on Cachexia Africana or dirt-eating, Amer. J. Med. Sci., XVII:365, 1835.
6. Cooper, M.: Pica, Charles C Thomas, Springfield, 1957.
7. Okcuoglu, A., Arcasoy, A., Minnich, V., Tarcon, Y., Cin, S., Yorukoglu, O., Demirag, B., and Renda, F.: Pica in Turkey, Amer. J. Clin. Nutr., 19:125, 1966.
8. Gutelius, M. F., Millican, F. K., Layman, E. M., Cohen, J. C., and Dublin, C. C.: Treatment of pica with a vitamin and mineral supplement, Amer. J. Clin. Nutr., 12:388, 1963.
9. Edwards, C. H., McSwain, H., and Haire, S.: Odd dietary practices of woman, J. Amer. Diet. Assoc., 30:976, 1954.
10. Edwards, C. H., McDonald, I., Mitchell, J. R., Jones, L., Visson, L., Kemp, A. M., Laing, D., and Trigg, L.: Clay and corn-starch-eating woman, J. Amer. Diet. Assoc., 35:810, 1959.
11. Stadtfelder, J., Einspruch, B., and Block, B.: The study of pica and food preferences in a post-partum general hospital population, Tex. Rep. Biol. Med., 18:202, 1960.
12. Richter, C. P.: Total self regulatory functions in animals and human beings, Harvey Lecture Series, XXXVIII:63, 1942, 43.
13. Richter, C. P.: The self selection of diet, Essays in Biol., Univ. of Calif. Press, 1943.
14. Davis, C.: Self selection of diet by newly weaned infants, Am. J. Dis. Child, 36:651, 1928.
15. McDonald, R., and Marshall, S. R.: The value of iron therapy in pica, Pediatrics, 34:558, 1964.
16. Ariete, S.: Interpretation of Schizophrenia, Brunner, New York, 1955.
17. Kanner, L.: Child Psychiatry. Charles C Thomas, Springfield, 1948.
18. Lourie, R. S., Layman, E. M., Millican, F. K., Sokoloff, B., and Takahashi, L.: A study of the etiology of pica in young children, In Problems of Addiction and Habituations, p. 74 by Hody, R. H. and Zubin, J., Grune and Stratton, Inc., New York, 1965.

19. Lee, D.: Cultural factors in dietary choice, Amer. J. Clin. Nutr., 5:166, 1957.

20. Pilgrim, F. J.: The components of food acceptance and their measurement, Amer. J. Clin. Nutr., 5:171, 1957.

Electrocardiographic Findings With Arsenic Poisoning

FREDERIC S. GLAZENER, M.D., *San Francisco*,
JOSEPH G. ELLIS, M.D., *Honolulu*, AND
PAUL K. JOHNSON, M.D., *Baltimore*

POISONING WITH ARSENIC preparations produces myocardiopathic changes which may be overlooked during the time the more dramatic gastrointestinal, renal, hematologic, neurologic, dermatologic or emotional effects occupy the clinician's attention. The electrocardiogram may reflect the toxic action of arsenic on the myocardium as prolongation of the atrioventricular or intraventricular conduction time, accentuation of after potentials, prolongation of Q-T interval and abnormal T-waves. Although non-specific electrocardiographic aberrations in themselves, prolongation of the Q-T interval and abnormal T-waves are seemingly so constant a feature of arsenic poisoning that we would like to emphasize these abnormalities in a case of acute arsenic ingestion and two cases of chronic arsenic poisoning.

Reports of Cases

Case 1. A 48-year-old married, male truck driver with a history of previous depressive reaction was admitted to the Veterans Hospital, Palo Alto, at 5 p.m. 12 Nov. 1963. At 9 a.m. he had drunk 75 ml to 100 ml of Ant-B-Gon, which contains 0.2 percent of sodium arsenite. The calculated arsenic trioxide equivalent of the ingested material was between 115 mg and 150 mg. Immediately regretting what he had done, the patient drank a quart of milk, and nausea and vomiting soon ensued. Vomiting and diarrhea, without blood, continued throughout the morning; and by noon he began to have cramping of the calf, thigh and abdominal muscles and in the intestines.

Reprint requests to: Out-Patient Service, Veterans Administration Hospital, 42nd Avenue and Clement Street, San Francisco 94121 (Dr. Glazener).

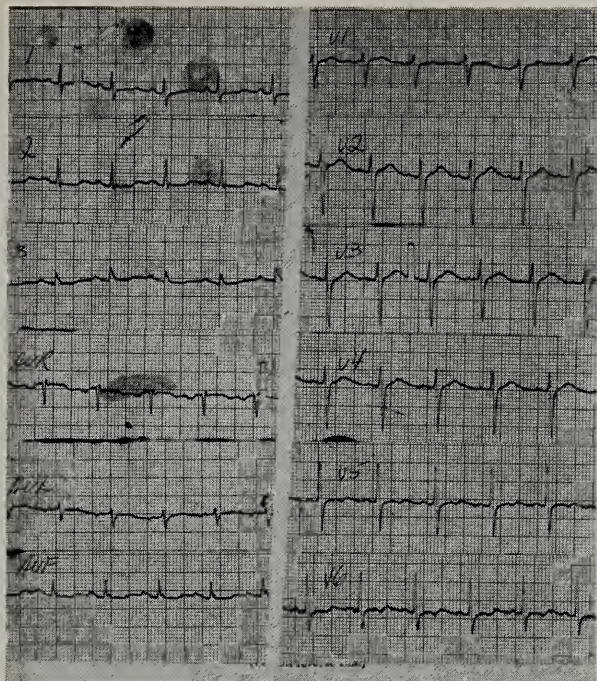


Figure 1.— (Case 1). Electrocardiogram four hours after hospital admission and 12 hours after arsenic ingestion.

When seen in the emergency room he was alert, oriented and remorseful. The leg and abdominal cramps had decreased in severity. Vital signs were as follows: Oral temperature 37.8°C (100° F); pulse rate, 100 per minute and regular; blood pressure 90/60 mm of mercury supine, 70/50 mm sitting. Moderate dehydration was evident. There was tenderness of the abdominal musculature and generalized abdominal tenderness, more pronounced in the upper quadrants. Incidental physical findings were inequality of the pupils and an undescended right testicle.

Initial laboratory studies showed the hematocrit to be 55 per cent; hemoglobin, 18.2 gm per 100 ml; leukocytes 18,600 per cu mm with a differential of 86 percent neutrophils, 8 percent lymphocytes and 6 percent monocytes. Specific gravity of the urine was 1.015, with 2 plus proteinuria, many granular casts and infrequent red and white blood cells. Serum electrolytes were as follows (values in mEq/L) sodium, 143; potassium, 3.9; chlorides, 118; and CO₂ combining power, 12.8. Blood urea nitrogen was 31 mg per 100 ml. Serum arsenic was 13.9 µg per 100 ml.* On the morning following admission, serum arsenic level was 17.3

*Arsenic determinations were done by a reference laboratory according to the method of Kingsley and Schaffert, *Anal. Chem.*, 23:914, 1951. Normal arsenic values for this laboratory are as follows: serum, 3.5-7.0 µg/100 ml; urine, 4.6-19.8 µg/100 ml; hair, 25-85 µg/100 gm; nail parings, up to 280 µg/100 gm.

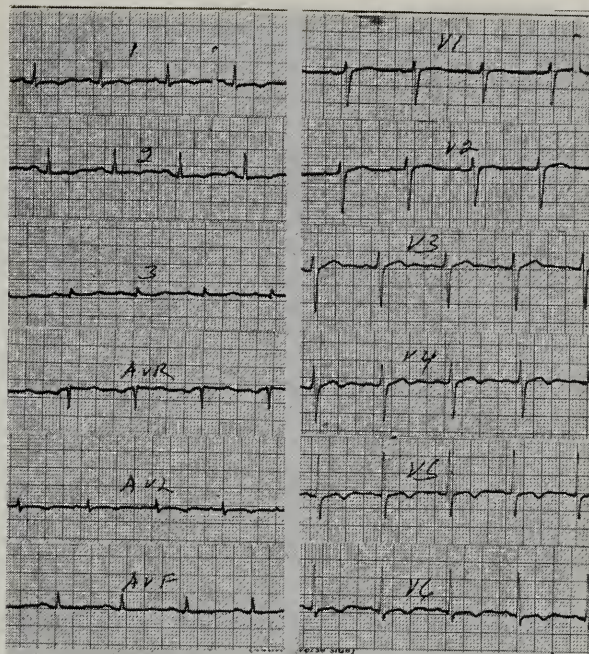


Figure 2.— (Case 1) Electrocardiogram 24 hours after arsenic ingestion.

µg/100 ml and urine arsenic concentration was 140 µg/100 ml. The SGOT was increased to 88 units. Serum creatinine was 3.7 mg/100 ml, and creatinine clearance was 42 ml/min. An electrocardiogram taken four hours after admission showed a rate of approximately 100 per min with abnormal T-waves and prolongation of the Q-Tc interval (Figure 1).

In addition to measures to correct dehydration, dimercaprol (BAL) was given, 3 mg/kg every four hours for two days, then two times daily for five days. Herpetic skin lesions and herpetic stomatitis developed on the fifth hospital day. BAL was discontinued on the seventh hospital day because of a diffuse, pruritic, macular skin lesion considered to be a drug reaction. An electrocardiogram on the day following admission after dehydration had been corrected and hypotension was no longer present, showed accentuation of the T-wave abnormalities (Figure 2). The tracing of 15 November exhibited some minimal T-wave improvement, and by 23 November the electrocardiogram was essentially normal. A follow-up tracing on 10 January 1964 was normal. At the time of transfer to a psychiatric unit on 29 November, arsenic was not detected in the serum, and the urine arsenic level was 50 µg/100 ml. Blood urea nitrogen, creatinine, creatinine clearance, SGOT and urinary sediment were within normal limits.



Figure 3.—(Case 2) Mee's lines of finger nails.

Case 2. A 37-year-old married man was admitted to the Veterans Hospital, Palo Alto, 7 July 1961 with complaints which included intermittent nausea and vomiting and tingling and numbness in the fingers. An x-ray film of the chest disclosed the presence of a coin lesion which had enlarged over a two-year period, and a thoracotomy with wedge resection of a coccidioidal granuloma of the right middle lobe was performed. Decided neuroasthenic symptoms persisted. Repeat physical evaluations disclosed weakness of the extensor and flexor muscles of the hands and feet, atrophy of the interosseous muscles, diminished tendon reflexes, and decreased appreciation of pin-prick and vibratory sensation in a "glove and stocking" distribution over the hands and feet. Touch and pressure over these regions evoked a delayed dysesthesia.

On 3 October the patient went home on leave of absence from the hospital but returned on 12 October complaining of nausea, vomiting and generalized muscular pain. There was now more distal muscular weakness and loss of tendon reflexes and sensation over the hands and feet. Fingernails and toenails showed the presence of Mee's lines (Figure 3). Laboratory studies revealed the hematocrit to be 35 percent; leukocytes 2,000 per cu mm; platelets 86,000 per cu mm. Serum electrolytes, including calcium, were normal. Arsenic poisoning was suspected and the following arsenic levels were obtained: Hair, 60 $\mu\text{g}/100\text{ gm}$; nail parings, 1.92 $\text{mg}/100\text{ gm}$; urine, 300 $\mu\text{g}/24\text{ hr}$.

A diagnosis of arsenic poisoning was made and a course of BAL therapy was given. Subsequently the patient's wife was committed to a mental institution. An electrocardiogram taken 13 July 1961 was a normal record aside from some doming of

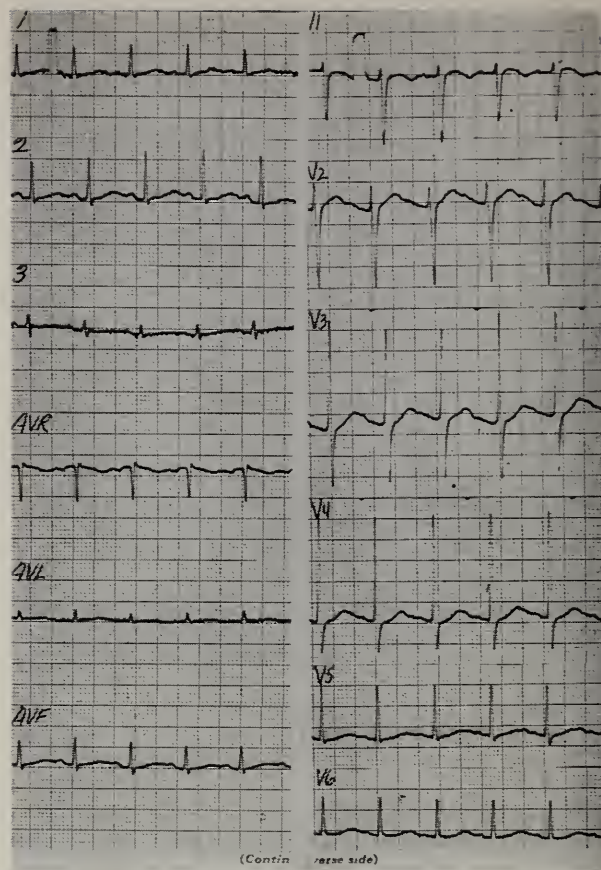


Figure 4.—(Case 2) Electrocardiogram at time of exacerbation of symptoms and physical findings.

the T-waves. At the time of exacerbation of symptoms and physical findings a repeat electrocardiogram showed prolongation of the Q-T interval and abnormal T-waves (Figure 4). A follow-up electrocardiogram was not obtained.

Case 3. A 46-year-old man with a history of previous psychiatric illness was admitted to the Veterans Hospital, Palo Alto, 12 May 1964 because of weakness in the hands and feet accompanied by tingling and burning sensations, a pruritic skin rash and laryngitis, all of three weeks' duration. Intermittent vomiting and diarrhea had been present for four weeks. On examination, profound weakness of the distal extremity muscles was noted, with loss of sensation in a "glove and stocking" distribution. Dysesthesia was present over the involved areas. Groups of excoriated papules with central necrotic crusts were scattered over the skin (Figure 5). Results of laboratory studies were as follows: Hematocrit, 26 percent; leukocytes 1,200 per cu mm; reticulocytes, 0.3 percent. The SGOT was 90 units. Spinal fluid examination and an electroencephalogram were within normal lim-

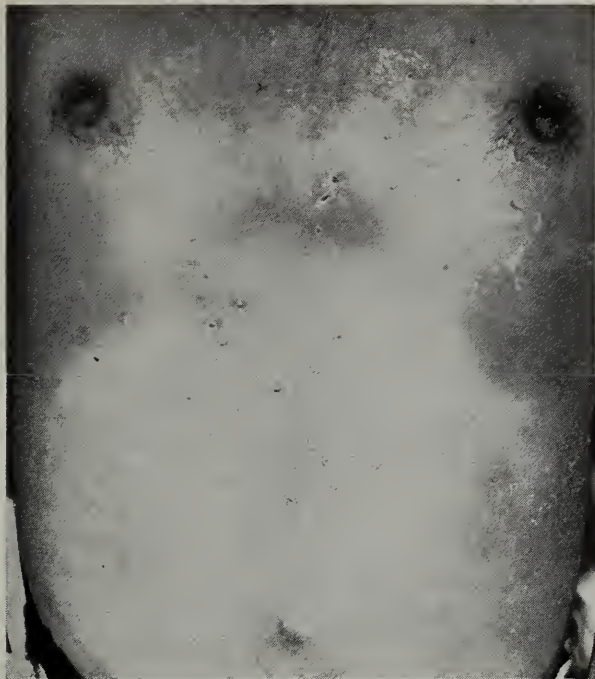


Figure 5.—(Case 3) Skin lesions.

its. Serum electrolytes, including calcium, were not remarkable. An electrocardiogram on 14 May showed prolongation of the Q-T interval, lengthened S-T segments, and abnormal T-waves (Figure 6). Arsenic poisoning was diagnosed and BAL therapy was begun after the following arsenic determinations were obtained: Nail parings, 2.61 mg/100 gm; hair, 0.59 mg/100 gm; urine, 124 μ g/24 hr. Classical Mee's lines did not appear in the fingernails until 65 days after admission (Figure 7). An electrocardiogram on 11 June was normal except for some increase of QRS voltage. An additional tracing three months later was normal. Although food was suspected, no definite source of the arsenic was established in this case.

Discussion

Probably the world's largest single series of cases of arsenic poisoning was reported by Hans Zettel, medical officer to the Luftwaffe.¹ In the latter part of 1941 a group of 170 young men belonging to a German anti-aircraft battery had symptoms, signs and toxicologic findings of arsenic poisoning. The source was traced to a contaminated water supply. Eighty patients had cardiac complaints, and serial electrocardiographic studies were done in these cases. Initially the most frequently noted electrocardiographic abnormality was prolongation of the Q-T interval; sometimes

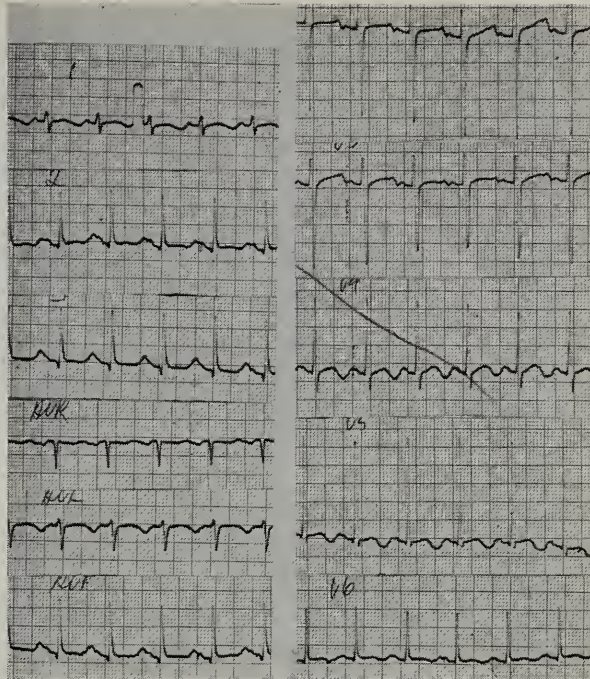


Figure 6.—(Case 3). Electrocardiogram showing prolongation of Q-T interval, lengthened S-T segments, and abnormal T-waves.

the T-waves were flat or inverted. Without specific treatment the Q-T interval in most cases had returned to normal by the end of six to eight weeks. By the end of three months there were significant electrocardiographic residuals in only two cases.

An electrocardiogram showing marked T-wave abnormality is included in the report of acute arsenic poisoning by Gousios and Adelson.² Although the Q-T interval is not mentioned, it appears to be prolonged for the rate. Weinberg³ recounted a case of acute arsenic poisoning with generalized T-wave changes in the electrocardiogram early in the clinical course. BAL therapy was given and electrocardiographic improvement occurred by the eighth day, with return to essentially a normal tracing by 14 days. A follow-up tracing 25 months later was normal. It was stated that no Q-T interval prolongation occurred; however, both the S-T segments and the Q-T interval are probably prolonged in the initial electrocardiogram. Barry and Herndon reported electrocardiographic changes in three patients with acute arsenic poisoning.⁴ They considered non-specific T-wave inversion with prolongation of the Q-T interval, primarily due to lengthening of the S-T segments, as characteristic but not specifically diagnostic changes of arsenic poisoning.



Figure 7.—(Case 3) Mee's lines.

In the three cases of arsenic poisoning herein reported, there were electrocardiographic changes similar to those reported previously. The most obvious prolongation of the S-T segments was noted in Case 3, and records of this type might be confused with the changes associated with hypocalcemia. In none of the cases could the electrocardiographic abnormalities be related to disturbances of the serum electrolytes; rather, they are considered due to a toxic effect of arsenic on the myocardium. Several years ago Peters showed protection of the pyruvate oxidation system against arsenic by dithiols. In a study by Rice and Berman⁵, decreased amplitude of contracting rat ventricle strips in a pyruvate medium and presence of arsenate was associated with an inhibition of pyruvate oxidation. Although arsenic has adverse effects on many enzyme systems, the inhibition of

pyruvate oxidation may be of significance in this instance.

The electrocardiographic changes produced by arsenic are generally reversible. Reversal is seemingly more rapid when BAL therapy is used than it was in Zettel's patients, who did not receive specific therapy.

Summary

The most commonly encountered electrocardiographic abnormalities associated with arsenic poisoning are prolongation of the Q-T interval and abnormal T-waves. Sometimes lengthening of the S-T segments occurs. In three cases of arsenic poisoning EKG abnormalities similar to those reported previously were found. In none of the cases could the electrocardiographic changes be related to disturbances of the serum electrolytes; they were considered due to a toxic effect of arsenic on the myocardium. Reversal of EKG abnormalities is more rapid when BAL therapy is used than when no specific therapy is given.

REFERENCES

1. Zettel, H.: Der Einfluß chronischer Arsenicadigung auf Herz und Gefäße, *Z. Klin. Med.*, 142:689, 1943.
2. Gousios, A. G., and Adelson, L.: Electrocardiographic and radiographic findings in acute arsenic poisoning, *Amer. J. Med.*, 27:659, Oct. 1959.
3. Weinberg, S. L.: The electrocardiogram in acute arsenic poisoning, *Amer. Heart J.*, 60:971, Dec. 1960.
4. Barry, K. G., and Herndon, E. G., Jr.: Electrocardiographic changes associated with acute arsenic poisoning, *Med. Ann. D. C.*, 31:25, Jan. 1962.
5. Rice, L. I., and Berman, D. A.: Oxidation of glucose-1-C¹⁴, glucose-6-C¹⁴ and pyruvate-2-C¹⁴ by contracting rat ventricle strips in the presence and absence of arsenate, *J. Pharmacol. Exp. Ther.*, 127:11, Sept. 1959.

A RULE OF LEG FOR HYPOVOLEMIA

"For patients who are indoors at ordinary room temperatures, a very valuable method of assessing hypovolemia is to run the back of the hand up the patient's leg from the toes to the groin. If the toes are warm, hypovolemia is not likely to be a problem. As the blood volume declines, the toes, then the feet and then the legs become cold. The zone between the cold area and the warm area is often surprisingly sharp—perhaps only an inch or two. As this zone of temperature change moves upwards, it generally reflects increasingly severe hypovolemia. . . . We calculated from hematocrit changes that a 30 percent decrease in plasma volume had usually occurred if the feet were cold, and perhaps a 40 percent decrease in plasma volume if the extremities were cold up to the knee level or higher. Admittedly, this is a very rough sign, but it is an extremely useful one."

JONATHAN E. RHOADS, M.D., Philadelphia
Audio-Digest *General Practice*, Vol. 16, No. 24

Health Data and the Physician

ERIC LEIGHTON, *San Francisco*

■ *California Health Data Corporation was formed to create better health data resources under the direction of hospitals and medicine. Highest priority is being given to developing information systems that will serve physicians, as well as those who are usually considered health data users. This is illustrated in CHD's first major activity, sponsorship of a medical record information system for California hospitals. This system is designed first of all to provide better information for medical staff committees, and as a byproduct to provide data flow into a CHD data bank. For the practicing physician, the significance of CHD is that the organization will attempt to develop information systems that will help the medical profession maintain its central role in guiding the present and future patterns of health care.*

A FEW MONTHS AGO the California Medical Association and the California Hospital Association together founded California Health Data Corporation (CHD). As stated in the CHD bylaws, the purpose of the organization is to "... assist public and private entities in California in guiding the present and future patterns of health care, availability and utilization of health facilities, professional personnel and other health services in California by engaging in the collection and dissemination of information."

Health Data Users

A physician ordinarily would not consider himself to be a user of health data. The designation instead calls to mind hospital planning agencies, fiscal intermediaries, or others of the variety of organizations that have assumed some kind of responsibility for overseeing medicine and health care institutions. These indeed are the professional users of health data, for data form the major part of their capacity for perceiving medicine.

It is intended that CHD will create better health data resources for these kinds of users, who have official roles in "... guiding the present and future patterns of health care." But CHD is pursuing another principle as well—that practicing physicians should be considered the most important users of health data. And this does not mean only the information quanta that a patient emits as the physician diagnoses and treats, but health data in the usual sense of numbers describing the health problems of individuals and of populations, and numbers describing the ways in which the health professions deal with these problems.

Most physicians will always be much more concerned about people than about numbers, but there are two important junctures at which any physician is likely to become a user of health data. One of these is in his personal assessment of his own practice over a recent period. At present, this most frequently takes place informally and intuitively, without much use of actual statistics. But information systems are now available which can enable an individual physician to use data and statistics to analyze his own patterns of practice.

The second situation in which physicians be-

The author is the Executive Director, California Health Data Corporation.

Reprint requests to: 655 Sutter Street, Suite 401, San Francisco 94102.

come users of health data, is when they have responsibility for evaluating the work of their colleagues. This usually occurs in hospital medical staff committees, although organized medicine is beginning to experiment with evaluation of care delivered outside the hospital. In most hospitals these committees work with a selection of charts rather than using abstracted data or statistics about groups of cases, but again there are information systems that can be very helpful to a committee by displaying patterns of care and enabling the committee to screen out only the really unusual looking cases for review.

One of the primary missions of CHD will be to bring information systems of this type to the service of physicians in California hospitals.

Measuring Quality of Care

It will be worthwhile to make a slight aside at this point, in order to discuss the use of data for measuring quality of medical care. Physicians often become rather uneasy when someone talks glibly about data, information systems and evaluating care—and quite rightly so. There is no doubt that many aspects of medical care are difficult or impossible to evaluate. Any interpersonal encounter as important as the physician-patient relationship will have attributes that cannot be found in textbooks. Even for well-defined elements of care, such as reading an x-ray film or interpreting an electrocardiogram, it is not at all easy to measure an individual physician's skills. On the other hand, it is very easy to tell whether a radiograph was taken or an electrocardiogram was made; and for certain kinds of patients this information would be an indicator of quality of care. There are many such criteria for adequate medical treatment that are not at all esoteric. Wherever there is agreement about what constitutes good medical practice, there quality of care can be measured, and there is need for data with which to perform that measurement. If it is agreed that one-unit transfusions should be rare, then statistics on one-unit transfusion rates for specified operations can be considered measures of quality of care, because they show the extent to which actual practice accords with an accepted standard. If it is generally agreed that most patients with acute coronary disease benefit from anticoagulant therapy, then statistics showing the usage of anticoagulants would measure this aspect of quality of medical care.

In spite of the rationality of this approach, the

statistical measurement of quality of care has generally been unsatisfactory to physicians, probably for the following reasons:

1. The statistics used as indicators of quality have been simplistic. For example, using a hospital's overall death rate as a measure of quality is rather pointless, since it includes so much variation due to diagnosis mix, a factor not under the control of the medical staff. The major reason for the use of inadequate statistics is that they have been the best that could be done without expensive special studies. This is one of the problems being overcome by new information system technology.

2. Even with the detailed statistics and the sophisticated manipulation of data that can be carried out with computerized information systems, the statistical measurement of quality treats medical care as if it were a collection of discrete hard facts, like marbles. As the physicist narrows his attention from molecular structures to the atomic and subatomic levels, he finds that his definitions of "wave" and "particle" no longer make sense; and as the physician particularizes his view from the level of statistics about groups of patients to one specific case, he finds that textbook abstractions are inextricably mixed with the unique attributes of the individual. The practicing physician knows through experience the level of uncertainty that exists in rendering care, and he knows by induction the level of uncertainty that therefore must exist in medical care statistics. The lesson is simply to let data and statistics serve where they will, knowing that at some level of detail the attempt to measure quality in discrete units will no longer be realistic. An important corollary is that practicing physicians should have the responsibility and prerogative for reviewing care, since only they will have the experience necessary to properly supplement statistics with non-quantitative considerations.

3. Most physicians have had too little experience in the use of medical care statistics. A physician considers a large amount of data in the course of caring for a single patient, ranging from statistics such as hemoglobin level to minimal clues such as gait, but he is usually unaccustomed to dealing with numbers about groups of patients. Part of the reason is that, as mentioned above, worthwhile numbers about groups of patients have not been available. But even when good medical care statistics are available, the physician sitting on a hospital's utilization or medical audit committee will

usually need to invest some time and energy in learning how to use these statistics. This is not to suggest that formal training in mathematical statistics is necessary, but there should be the willingness and opportunity to learn through experimentation.

4. Finally, the measurement of quality of care has too often been identified with punitive or regulatory functions. When medical care data is seen only as ammunition for an individual or group sitting in judgment, the physician being judged will naturally be reluctant to supply any more data than is absolutely necessary. On the other hand, if medical care statistics are seen primarily as a method of informing the practitioner, so that he has the opportunity to make his own judgments, then there should be a good deal less anxiety. Moreover, those who do have responsibility for review—such as a medical audit committee—can make a more relaxed and realistic use of statistics for educational purposes than they can if they feel they have to build a case against somebody. Undoubtedly, both regulatory and educational approaches will always be needed, but many physicians have had bad experiences, either on the giving or the receiving end of criticism, because the educational approach has not been given precedence.

To recapitulate, we have been asserting that the statistical approach to measuring quality of care can be valid and productive, providing that (1) "quality of care" is defined in terms of accordance with accepted standards of practice, (2) sensibly constructed medical care statistics are available, (3) these statistics are used by practicing physicians at the source of the care being studied, (4) these physicians have developed some facility for working with numbers as well as with charts, and (5) the evaluation process is part of educational feedback to practitioners rather than only a regulatory function.

CHD's Medical Record Information System

The dissertation in the preceding paragraphs was intended to give some of the rationale behind the first major activity of California Health Data Corporation: sponsorship of a medical record information system for California hospitals. The system—known as Medi-Record—automates many procedures of hospital medical record departments. It works this way:

1. From the chart of each patient discharged, the medical record librarian abstracts the most important data. This takes an average of two minutes per chart. (No extra paper work for the physician is involved.)

2. The case abstracts are mailed to a computer center, where the hospital's necessary medical record indexes and statistics are prepared.

3. The computer output is mailed back to the hospital, providing more information at lower cost than with hand methods.

This is a very simple and inexpensive approach to automation, but it goes a long way to improve the utility of medical record information. As well as the obvious utility to medical record librarians, following are the benefits for physicians:

1. At the *individual* level, each physician on the staff receives each month a listing of the patients he has attended. This listing amounts to an inventory of his patient load, and shows the name, age, sex, diagnosis, operations, affiliated physicians and other information for each patient. The listing also shows which of the patients have been referred to medical staff committees.

2. At the *institutional* level, the system produces each month a list of charts to be referred to committees. The selection for this listing is based on certain basic criteria—deaths, patients with transfusions, patients with complications, etc.—plus whatever other criteria the medical staff may specify. These additional criteria are fed into the system by the medical record librarian at the time of abstracting.

The system also produces disease and operation indexes in a format particularly helpful for utilization review. For each disease and operation, these reports display the case abstracts of individual patients followed by detailed length-of-stay statistics for the group. This structure enables a utilization committee to see the typical length-of-stay patterns in its own hospital, to find the cases in which there is atypical stay, and make an initial evaluation of those cases from the computer-printed information, before pulling a chart.

We started development of CHD activities with this medical record system because it is the kind of information system that serves our purpose of making the physician a user of health data. With Medi-Record and a competent medical record librarian to serve as an information retrieval specialist, committee work can become much more effective without requiring additional time. In

fact, any hospital that is now preparing medical record indexes and statistics by hand is depriving its medical staff of an essential information tool.

There are now one hundred California hospitals participating in the CHD medical record system, and the number is growing steadily. It has been well established that the system generally adds no cost to hospital operation, requires very little change in present information-handling procedures within the hospital, and can be implemented quickly and easily.

A Medical Audit Information System

Medi-Record is a good basic system as it stands, but we have definite plans for increasing its utility to hospital medical staffs. The first step will be to expand its capacity for recording details of medical care, such as types of x-rays taken, laboratory tests performed, drugs used, and types of therapy employed. This increased data input would still be handled in the medical records department, and would not require any change in charting by physicians.

The next step will be to make the computer more responsive to the specific needs of medical staff committees. This might work in the following fashion:

1. A hospital's medical audit committee would select a category of patient for study, such as acute coronaries. The committee would proceed to specify criteria—its own criteria for its own hospital—that would define excellence in the care of patients with acute coronary artery disease. These criteria might be stated in the following way: all patients should have two electrocardiograms or more, most should have anticoagulants, the death rate should be less than 15 percent, and so forth.

2. These criteria would be recorded in a format easy to transfer into a computer program. This would probably be done by the medical record librarian, who would know how to relate the committee's criteria to the appropriate items in the data file. The criteria would thus become specifications for data processing activity.

3. The specifications would be sent to the computer center, where they would be introduced directly into the computer system. Acting as a "super-clerk," the machine would be put to work on that hospital's accumulated data for acute coronary disease. The output might include certain statistics tabulated for the entire group of patients,

an "exception listing" of individual cases not meeting the committee's criteria, and a complete listing of all the cases showing specified items of information about each.

4. At the next meeting of the medical audit committee, the group would be working with an information display prepared by the computer to their own specifications.

This kind of manipulation of data files is perfectly feasible with today's computer technology. One of the benefits of this approach is that it forces physicians to be logical in their specification of criteria for good quality care. The most important benefit, however, is that such a system would enable medical audit committees to experiment with statistical criteria. For example, the committee might initially ask what proportion of the total had received anticoagulants. Upon seeing this statistic, however, they might realize that they want to have this anticoagulant rate for each physician as well as for the entire group. This change in specification could be resubmitted to the computer center, and in the next report cycle to the committee the reports would be altered accordingly.

With this kind of interchange between theoretical criteria and actual data, a medical audit committee could develop specifications for continuous computer screening of various disease entities, to decide which cases should be referred to the committee for more detailed review. This is exactly the way a computer should be used—under the control of the people whom it is intended to serve. This would in fact be a true medical audit information system, with optimum balance between man and computer.

Cost of Medical Care

Certainly the most public issue in medicine today is the rapid rise in the cost of medical care, particularly hospital-centered care. Indeed, this appears to be a problem which has had the rare effect of uniting government, management, labor and the mass media in a very critical attitude toward physicians and hospitals.

As could be expected, one of the goals of CHD is to create data which can help us understand why costs are rising and what can be done about it. Our work toward this goal is based on the following premises:

1. Considerations about cost of medical care cannot be separated from concern about quality of medical care. No thinking person wants economic

anxieties to lead to changes in the health care system that would jeopardize our present high level of care.

2. Real progress in our attempts to control costs will come only when we have the ability to relate medical care costs to specific types of patients. If we hope to have rational expectations about what the costs for a given hospital ought to be, those expectations will need to take into account the mix of medical care problems represented by that hospital's patient population.

For these reasons we started CHD activities with a program for collecting data from medical records, even though there are virtually no cost data involved at the present time. Medi-Record (and the medical audit information system now being planned) provides capability for maintaining surveillance of care, in line with the first premise above. Moreover, Medi-Record provides data about each patient and thus can be used to generate statistics showing the specific patient mix in each hospital, in accord with the second premise stated above.

As a first step toward gathering cost data we will recommend that hospitals record the total patient bill on the Medi-Record case abstract for each patient. We recognize that the total bill for a patient has only a tenuous relationship to the total costs incurred for that patient, and, further, that that relationship will vary considerably from one hospital to another. Even so, interhospital comparisons of charges related to disease groups will provide very interesting and useful information.

To have more detailed cost data, we will need to pick up these data from the billing, accounting and payroll procedures within the hospital. This will be a much more complicated process than data acquisition with Medi-Record, where the data is abstracted from a single, complete and well-organized file. More and more hospitals, however, are using computer systems for business office functions, and such systems should make it relatively simple to accumulate and save for retrospective analysis the necessary data about each patient.

We are also aware of the need to gather similar kinds of data from other places in which medical care occurs—outpatient departments, clinics, physicians' offices, nursing homes and extended care facilities. It is too early even to surmise what systems for data acquisition will prove practical for these sources, but we will continue to give

highest priority to systems that can help practicing physicians maintain surveillance over patterns of care.

Health Data Bank

Most of the above discussion has been about the present and potential benefits of the CHD medical record system as it can be used in the individual hospital. There is another dimension to CHD's purpose in sponsoring Medi-Record: the development of a health data bank.

When a hospital participates in Medi-Record, the data recorded for its own reports is also permanently stored on magnetic tapes. This creates continuous accumulation of data that can be used to produce interhospital comparisons and statistics representing patterns of practice for given geographical areas. For the practicing physician, this would have value in enabling the production of a kind of textbook of actual medical practice (in contrast to the usual textbook which intends to represent ideal practice). Comparative statistics should never be used as standards, of course, but they can enable a physician to understand his own practice better through contrast with that of others. One of the legitimate concerns about data banks is that they may be used to invade the privacy of individuals represented in the data. In recognition of this problem, one of the first actions of the CHD board of directors was to establish the following policy:

1. The data in the CHD files belong to those from which it came. No information about a hospital will be released to any individual or organization unless there is written authorization from the hospital administrator to do so.

2. Data from the CHD medical record system will be purged of physician and patient names before being transferred to the permanent data bank. (Indeed, hospitals may elect not to record these names in the first place; they are part of the Medi-Record system only for the convenience of users within the hospital.)

3. All provision of information from CHD data files, whether or not the identity of hospitals is involved, must be approved by the CHD board of directors.

The purpose of the CHD data bank is to create the technical capability for information sharing, but the manner in which information is shared (or whether it is shared at all) will be under the control of each participating hospital.



The Scope and Responsibility of Medicine

A Forum with a Purpose

To engender discussion of what the scope and responsibility of medicine ought to be in today's society, CALIFORNIA MEDICINE printed in its June issue six essays by authors known to have keen if various interest in the subject.

In presenting the essays the editors expressed hope that they would be the beginning of a forum from which a definition of our profession's responsibilities may be distilled. Readers were invited to take part in a continuation of the forum in succeeding issues. Following are three contributions selected from those received to date. Others will be published in the months ahead.

If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102. Keep your essays short, please.

JAMES W. HAVILAND, M.D.

Seattle
Member of the American Medical Association Council on
Medical Education

I FOUND THE discussion of the Scope and Responsibility of Medicine very interesting and have read all articles in considerable detail. Dr. Mellinkoff seems most nearly to have caught the broad perspective conjured up by the title. I would like to suggest the following formulation as perhaps aiding and a bit helpful in furthering the discussion of this general subject:

1. Individual physicians are simply individual human beings who have obtained excellent specialized education and have developed corresponding skills. They have no innate qualities which set them apart from or above other human beings.
2. Medicine is the creature of society. It provides for or responds to the demands and needs of society. (cf Sigerist)
3. Society defines the "scope" of medicine. Society makes its informed or educated decision based in so far as possible on facts. Physicians participate in this decision-making as informed citizens. (They function quite apart from providing health services.)
4. Medicine's "responsibility" follows thereafter; name-

ly, to try to provide the manpower facilities or other requirements to meet the demand generated within the scope of the problem as defined.

5. It seems to me that much of today's uncertainties in medicine stem directly from the dislocations which have been forced on us by the abrupt transition dictated by legislation which takes us from a concept where medical service is available in the traditional manner of the past seventy-five to a hundred years to the current philosophy that health service is available to all as a right. In part, one might say that today's troubles reflect society's failure to reach a consensus. Even now, many individual groups both inside and outside medicine are still striving to force their concepts and beliefs of "scope" on the entire population. Certainly medicine's experience and "know-how" can and should be mobilized to help develop appropriate decisions. In this decision-making process, one would hope that there would precipitate out much of the extraneous material now floating round and round thus leaving "hopefully" a rather clear solution in place of the muddled cross-currents of conflicting opinions and proposals which exist at the present time.

Thanks for the opportunity of letting me express myself on this interesting topic and I wish The Forum every success.

EINAR O. MOHN

*Burlingame
Chairman, California Council for Health Plan Alternatives;
International Director, Western Conference of Teamsters*

OUR SOCIETY is now much concerned with the secondary symptoms of its overall health care problem. We spend a disproportionate amount of time on financial and administrative arrangements, and on re-shuffling the same deck of scarce resources, including both manpower and facilities. Questions on "the scope and responsibility of medicine" are seldom even raised. When they are, we would do well first to dispense with most of the jingoism used as daily stock in trade, especially the catalog of arguments about costs, but most of the book on "quality" as well.

To clear the air in this respect, assume a theoretical point: that physicians of all specialties, working in every kind of practice and in every kind of research or administrative situation, would be allowed to draw any amount of income they desired from a central fund of both private and tax monies—a fund especially created for the purpose. Assume further that there are sufficient monies in the special fund to satisfy all demands. Assume further that all major arguments about how the monies are raised for this special fund have somehow been compromised and resolved. (Ironically the final assumption is the most theoretical of the three!)

The first result of this new state of affairs, in my opinion, would be to create tremendous pressures for increasing the supply of doctors. The main pressure would come from the profession itself. Money (and social status) aside, other things become much more important, and most "other things" require the use of limited time. Of course, there would be no shortage of qualified applicants asking for admission to the sacred order, and the resulting pressure for expanded educational facilities and opportunities would have to be met.

The second, and more important result, it seems to me, might be to make it possible to move beyond what John H. Knowles has described as "the present defensive isolation of the medical world in its bastions of acute curative, specialized and technical medicine, the hospitals . . ."

If the medical profession responded more often to our health care problems, and less often to the financial considerations involved in different methods of providing care, then it would at least be possible for us to acknowledge our many problems and shortcomings, such as, (a) the failure to develop adequate systems for preventive care; (b) the failure to make health care comprehensive in most existing delivery systems; (c) the failure to bring adequate care to the impoverished who are most in need of it; (d) the failure to develop services on a planned community basis, and to extend them into the home when necessary. Our failures in mental health, and in both physical and mental rehabilitation, are abysmal examples. We have only the merest beginnings of health care programs in some of the nation's ghetto areas, and even the modest Headstart attempt is being cut back drastically.

In the meantime, the successes of the "star performers" on the transplant teams are widely heralded as the finest examples of our technically masterful specialization in acute care. Only an occasional question is raised about the broader responsibility of the profession to the much more mundane and everyday health needs of thousands. (This is one implication in the current wry story about the first, dramatic, successful transplant of an appendix!)

Health care is one of the most challenging social problems of our time, but simply to recognize it as a social and not just as a technical problem is perhaps the greatest challenge of all. This is not to argue that the profession should take leadership in the solution of problems of poverty, urban decay, minority oppression, inadequate housing, or underdeveloped nations. It is to argue that the same "social welfare" implications that give these other problems their present degree of urgency, now give the health care problem the same kind of urgency. And it is to argue that new approaches of a truly social nature are urgently needed, and should not be chopped down

by entrenched economic interests, or by social and political philosophies more appropriate to another period of history.

As a practical matter it may be too much to expect the medical profession actually to give meaningful leadership to the needed development of comprehensive community health care agencies, staffed with personnel trained for a "social preventive" approach, and using neighborhood-based teams combining many skills and areas of knowledge. It is not a simple matter even to encourage some movement away from medicine's predominant emphasis on the acute, highly specialized hospital care.

As an alternative, it may yet be necessary to "buy-off" those incumbent professionals who refuse to recognize the need for change, with money, or leisure, or research freedom, or perhaps with some new kind of social status to be invented for the purpose. The theory of this approach would be that others could then be trained to meet the larger responsibilities of improving community health. Some large corporations follow this line of least resistance in their treatment of top policy people who are no longer effective.

It is to be hoped that the latter kind of alternative will be unnecessary; that the most responsible members of the medical fraternity will join with responsible leadership from many other walks of life to find answers to the current health care crisis and that it will be possible to devise effective new health care systems going beyond the sacred concepts of solo, fee for service, free enterprise, closed door, private office, private practice. In short, it is to be hoped that it is still possible to develop evolutionary adaptations which are sufficiently "radical" to meet the social needs of our times, without the upheavals and the chaos usually accompanying rapid change.

RUSSEL V. LEE, M.D.

*Palo Alto
Consultant, Palo Alto Clinic*

HEALTH, AFTER SALVATION, is the most highly prized boon for mankind. And for many whose hope of salvation is perhaps a little dim, it is the first objective. For the individual, it is the principal component in the achievement of happiness and efficiency. For the nation, it is the principal component in the achievement of national strength. In the past the achievement of health was made possible in a variety of ways by a diverse group of people. Purely empirical guides were followed. But now the attainment of health is assured by the application of scientific discoveries to the problems of living. In the application of these known scientific principles for the attainment of health, medicine which once was unimportant is now predominant. The scope of medicine is the health of individuals and of the nation. The responsibility of medicine is to make sure that everything possible is done to achieve and maintain health for all people.

There are eight principal components necessary for the achievement of health. These are: 1. Promotion of Health; 2. Prevention of Disease; 3. Diagnosis, Treatment and Rehabilitation of the Sick and Injured; 4. Medical and Health Education; 5. Research; 6. Supplies and Facilities; 7. Organization of Health Services; 8. Governmental Participation. In each of these medicine plays an important part. In some it is almost solely responsible.

1. The Promotion of Health

Although this is the most important, it is often the least considered component. In our enthusiasm for the miraculous new advances in the science of medicine we often overlook the fact that the health of mankind was improving spectacularly before these discoveries. This improvement was due to a raising of the standard of living. Proper nutrition, proper housing, proper clothing,

proper environment contribute basically to health and must be available if medicine is to have a chance to function properly. Vitamins are fine, but not so vital as food. The promotion of health is an activity in which all elements of society must participate. Although most of the effort made to promote health must be by others, medicine has a great responsibility in this field. First, it must by observation, study and research determine just what promotes health and what is deleterious. Then, armed with this knowledge, it must direct the general effort into effective channels. And finally, it must participate directly in the task of assuring good food, good housing, good education and good environment to all. Medicine must not shrink from political pressure and action when they are indicated. Medical students should be given a more accurate understanding of the concept of the promotion of health.

2. Prevention of Disease

Everyone knows it is even better not to get it than to be cured. The prevention of epidemic disease has been perhaps the greatest achievement of all time in contributing to the health of nations. Cities, armies and our great technical achievements depend upon it. Medicine can be proud of the part it has played in this great victory. Most of the discoveries that made it possible were made by physicians, not infrequently at great sacrifice and with great heroism, as in the case of Walter Reed. Necessarily, because of the nature of the problem, most of the administration of preventive health measures must be in the hands of governmental agencies. But medicine must assist these agencies in every possible way as, indeed, it usually has, paradoxically destroying, in a sense, its reason for existence. We need more cooperation; we need more money for public health so that we can pay salaries sufficient to attract good men into the field. Medicine should urge more financial health for public health. We should recruit more young men and women into this branch of medicine. There are hundreds of unfilled places in public health.

Medicine should actively sponsor and promote the relatively new field of personal preventive medicine—to find out and then to persuade people what to do to prevent illness. The campaign against cigarette smoking is a case in point. There are many others—obesity, exercise, proper immunizations, proper diet all fall into this category. There is much we need to know but much we do know we do not apply. Medicine must be a constant and vigorous propagandist in this field.

3. Diagnosis, Treatment and Rehabilitation

This has always been and still is the area in the health field where medicine has been predominant. In recent decades the advances have been impressive. But still, as in many branches of the health field, the gap between what we know and what we do is growing wider. The increased demands for medical services, because they are universally recognized as being essential, without a corresponding increase in health personnel has deprived many of access to health care of high quality. Then, too, the advances have been so rapid that many doctors completely occupied with patient care have failed to keep up with progress. Medicine needs to devote much attention to the adult education of the physician. Reexamination at ten-year intervals may be necessary. The humanitarian potential in the field of rehabilitation has been neglected. Much progress has been made in theory but lamentably little application has been made of it. The rapidly increasing number of elders indicates that more attention is needed in the field of geriatrics. In general, patient care in this country is very good indeed but it could be superb.

4. Medical and Health Education

Part of the Hippocratic Oath enjoins the physician to teach his art to those who would learn. We have done badly in this regard in a quantitative sense. Organized medicine that did so much, after the Flexner Report, to improve the quality of the medical schools actually opposed increasing the numbers of physicians as recom-

mended in the report of the Truman Commission on medical care. Now we import 25 percent of the new doctors who start practice each year. As the most affluent country in the world, we should export thousands of trained physicians to the underdeveloped nations. The education of physicians is done well, and innovations in the curriculum are constantly being made, but little progress is made in increasing the numbers. Medicine also has the responsibility for increasing the numbers and the quality of paramedical personnel who could do much to ease the burden of shortages if they were available.

The education of the people in matters of health is almost as important as the education of medical personnel. A well-informed man lives a healthier life, and knowing the benefits of good health care sees to it that he and his family get it. Television and radio and periodicals furnish the means to make this country well informed in matters of health. Medicine should initiate, sponsor, and actively participate in programs of health education for the public. Actually, not due to any organized effort by medicine, the people are really quite sophisticated in health matters although, as always, quite gullible for quacks and impostors.

5. Research

The dollars spent on medical research have paid larger dividends than any others. Penicillin, if kept exclusive by patents, was worth at least twenty billion dollars. We have done well in this field and medicine has played a significant part in it, first through the work of brilliant individuals and then by organizing for projects which required groups working in unison. The National Institutes of Health has been one of the greatest institutions in our history. But we must continue to do three things. First, recruit, develop and nourish workers in the research field; second, support appropriations for this purpose; and, third, participate individually in clinical research incidental to our regular daily work. This last component, clinical research, lags behind basic research, and can only be done by doctors who are actually engaged in patient care. But we must see to it that, under the banner of governmental economy, research is not starved of the funds needed for its continued brilliant achievements.

6. Supplies and Facilities

The genius of the American people for production has assured us ample supplies (at a price). The production of new drugs and their exploitation to physicians is perhaps a little overzealous. We must support the fine efforts of the Federal Drug Administration in this regard. The new field of electronic devices needs careful supervision and development with a new kind of collaboration between physicians and electronic engineers.

The physical plant—clinics, hospitals, laboratories—is, by world standards, pretty good. But in the light of what we have learned in the past ten years, the physical plant is antiquated and needs almost complete replacement. A tenth of the money spent on the exploration of space would do just this. Medicine must raise its voice as to the proper allocation of national expenditures. We can afford and we should have a modern efficient plant.

7. Organization of Health Services

Despite our national genius for organization, we have been woefully deficient in the proper organization of our people and our facilities to produce the utmost efficiency in the health field. The new role of the hospital, the real advantages of group practice, the device of voluntary prepayment rather than state medicine all call for organizing ability of the highest order. It is abundantly apparent that one alternative to governmental controls is the voluntary, organized and locally controlled community health facility, staffed by group practice, employing many paramedical workers and based on a cooperative prepayment plan. There are of course other devices for other purposes. But with our shortages of trained people the organization of health services in a rational manner is urgent. The alternative will be state medicine.

8. Governmental Participation

Because of its importance to national strength no modern government can neglect the health of its people and stay in power. The participation goes all the way from a cursory control of public health to complete state medicine which has taken over so much of the world. But everywhere governmental participation increases. It is the responsibility of medicine to guide, rather than be led, in this inevitable process. Our attitude must not be negativistic but rather cooperative. A synthesis of the state and private components is possible and offers the best chance for the future. Medicine must accept the necessary role the government will play but at the same time preserve

the benefits that come from private initiative and competition.

Conclusion

The tremendous impact of medicine upon society imposes great responsibility on medicine. The very existence of mankind depends on medical success—such problems as an insupportable population explosion, widespread starvation, degradation of our genetic inheritance, are in the scope of medicine's interest. Never before has the role of medicine been so potent and so great. And yet our prestige has gone down. We must regain the high place we once held by a demonstration of zealous, intelligent devotion to the public welfare. That is what medicine is for.

THE UNSCRUPULOUS HEARING AID SALESMAN

"My pet hate is this: Hearing aid salesmen who might as well be selling used cars or neckties, but who have the audacity to believe that, because they are working in a paramedical science, they have all the rights of that science with none of the responsibilities. You send a patient to a hearing aid salesman whom you don't know and often the patient will come back and report that the salesman wants to sell him *two* of them—and with that kind of salesman if he could find one to stick up the nose or in the belly button, he'd sell *four* hearing aids. Do you have any idea how many hundreds of thousands of hearing aids are lying in closets doing nothing? And each one of them costs \$300 or \$400—money from people who most of the time can ill afford it. Don't allow these people to be exploited by salesmen. The overcharge is unconscionable. Be sure that you let the hearing aid dealer know: 'Mister, this is your opportunity. This is your trust. You violate it, and you'll never see another patient of mine.' "

—LESTER COLEMAN, M.D., New York City
Audio-Digest *General Practice*, Vol. 16, No. 25



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EDITORIAL

Let's Turn On!

SOMETHING OF UNUSUAL importance may have happened at the convention of the American Medical Association in San Francisco. Only time will tell whether medicine found a unity, an inspiration and a sense of purpose in this beautiful city that is so vibrantly alive. Quite properly, the House of Delegates was the scene. The incoming president of the AMA, the president of the Student AMA (SAMA) and a frustrated spokesman for a poorly identified "Medical Committee for Human Rights" were among the principal players. The script was impressive. The message was one of vision, energy and optimism for the future of American medicine and for its principal aim, "The betterment of the public health."

No physician or student of health care should fail to read and ponder the meaning of the two extraordinarily perceptive statements of Dwight L. Wilbur to the House of Delegates. They were entitled "Emphasize Steering Instead of the Brake" and, a more detailed commentary, "Cockroaches and Cherrystones." Both have been published in the *Journal of the American Medical Association*.^{*} C. Clement Lucas, Jr., expressed the deep social commitment and very positive activism of today's medical students with feeling and conviction. And, largely unheard (the microphones were not working at the time) was the uninvited

spokesman for a "Medical Committee for Human Rights" who surprisingly echoed much that the others were saying, if one ignores his infatuation with compulsory medicine and his equally outmoded cries of racism and discrimination.

Quite unexpectedly, what comes through in all four of these statements is a deep reaffirmation of the humanitarian goals which have always been medicine's reason for being, and a conviction that these must now be pursued by the profession with new energy and new action—with a new *activism*, if one use the language of the day. It seems most significant that these expressions reflect both youth and experience within the profession, and both the "ins" and the "outs" as far as organized medicine is concerned. This constitutes quite a remarkable unity.

It remains to be seen whether the message was heard or whether a significant new professional activism will in fact come into being. There is surely nothing novel about humanitarian goals in medicine, but there is a lot to be learned and a lot to be done about the technology of achieving these goals in modern society. Practicing physicians and organized medicine have long been activists in the technology of medical science. An entirely comparable activism on the part of the medical profession is now needed in the technology necessary to achieve the humanitarian and economic goals of health care in this great nation. And, just as is the case with medical science, this can best be done in collaboration with others of like purpose, whether in or out of government.

The message from San Francisco is that such a new activism on the part of organized medicine could "turn on" the young physicians, mobilize hitherto untapped sources of energy and bring

^{*}JAMA, 205:89-96, 8 July 1968.

about a real unity within the profession. Let us hope that under the present AMA leadership the process will at least begin.

Treatment of Acute Leukemia

FOR THE CLINICIANS and investigators who thrive on therapeutic results, the field of cancer chemotherapy has been frustrating indeed. Of the great number and variety of patients with malignant disease, only a small fraction are benefited by medical means. Even rarer are examples of such prolonged control that the concept of cure by drugs can be considered.

The glimmer of hope in this difficult field began 20 years ago with small advances in the treatment of acute lymphoblastic leukemia of childhood. Gradual improvement in results effected by a wide variety of therapeutic agents and the proper use of supportive measures allow one to be convinced that useful life can be prolonged, that agents can be directed toward specific sites of the cell cycle, that rational combinations and cyclic chemotherapy can be conceived and that true cures have been observed and more projected.

The review of this subject by Doctor Cline in the U.C. Medical Staff Conference emphasizes the state of our knowledge and some of the challenges that face the clinicians and investigators involved in the management of acute leukemia. It should be added that the encouraging results and considerations in the treatment of acute lymphoblastic leukemia of childhood have, in large part, been responsible for the development of the entire field of cancer chemotherapy. The proved curative value of chemotherapy in the treatment of choriocarcinoma in the female and possible curative value in the treatment of Burkitt's lymphoma, Hodgkin's disease, and Wilms' tumor have been developed to some extent through the lessons learned from the treatment of acute leukemia.

It is worth emphasizing one of Doctor Cline's points, however. The chemotherapy of acute leukemia should be undertaken only by individuals and centers experienced with the management of these disorders, not only because the therapeutic programs can be so difficult and complex, but also because with the proper use of today's available agents and supportive measures the results can be so very good.

Prevention of Ischemic Vascular Disease

IN THIS ISSUE, Frederick T. Hatch argues persuasively that the physician must become more involved in programs to prevent ischemic vascular disease resulting from atherosclerosis. It is clearly feasible to alter some of the factors that have been associated unequivocally with risk of developing coronary heart disease. If such alterations will in fact substantially reduce the incidence of this disease, we have a clear example of a gap between basic knowledge concerning a major disease and its application. That physicians have not so far approached this problem systematically largely reflects doubt that such measures will be effective. "Experts" speaking on this subject are invariably asked whether they really believe that reducing the level of serum cholesterol or other lipids will make any difference in a disease whose cause is considered to be multi-factorial. Accumulating evidence favoring such a belief is cited by Doctor Hatch as well as our almost astounding ability to identify risk of developing coronary heart disease (at extremes we can identify a middle-aged man with 15 to 20 times the risk of having a myocardial infarction as another). With this knowledge, we need to ask ourselves whether we can afford to wait for conclusive proof that we can alter risk. Is the evidence that we can postpone vascular complications in patients with maturity-onset diabetes by lowering the blood sugar more (or even as) convincing than the evidence that heart attacks can be postponed by reducing the level of serum cholesterol?

In order of importance and, perhaps, feasibility, appropriate measures appear to be reduction or cessation of cigarette smoking, loss of weight (what did you weigh when you were 20?) and a regular program of muscular exercise. These recommendations can logically be applied to all. A really effective program must, however, go beyond this. It will be necessary to develop efficient methods to identify the apparently healthy individual at high risk and to apply measures tailored to his problems. This involves chiefly identifying the presence and type of hyperlipidemia and of arterial hypertension. Elevated levels of lipids or blood pressure can at least partially be corrected in almost all cases. Doctor Hatch stresses the fact that we have not yet developed effective ways to apply such procedures and know remedial measures widely.

Personnel and facilities made available through the Heart Disease, Cancer and Stroke Program should be used to help learn how this can be done. One possibility is to develop appropriate centers or clinics in our communities to which the physician can refer patients with hyperlipidemia or hypertension for assistance in evaluation or management. This should be coupled with programs to educate the public and especially physicians who are in a position to evaluate and treat subjects at high risk.

As we enter the era of cardiac homotransplantation with its extraordinary demands in cost and personnel, can we afford to ignore the reasonable possibility that we can decrease the need for such drastic measures?

Health Data

ACCESS TO DEPENDABLE facts is an absolute essential for any rational approach to the betterment of health and health care. For the facts of medical science this has been long and well recognized, and the most complicated professional arrangements exist to bring the most recent information of scientific progress to scholars, teachers and practitioners of medicine. Far less attention has been given by the profession to the collection, storage, dissemination and use of reliable data concerning other than the purely scientific aspects of good health care. Much of what has been done about data of this kind had its origin in California.

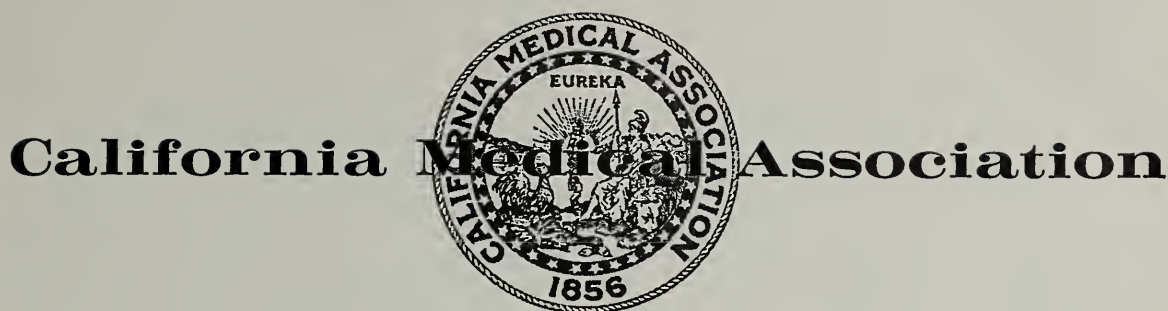
Health care here and throughout the nation owes much to the dependable facts garnered by the widely regarded Bureau of Research and Planning of the California Medical Association, which was one of the first organizational instruments in American medicine to be dedicated to this essential purpose. It is still one of the very few in existence. Another debt is owed to those who collected the reliable data which have given valid substance to the California Relative Value Studies and made possible many of the important innovative programs of California Physicians' Service, now called California Blue Shield (C.B.S.). Most recently, dependable facts from C.B.S. tapes and elsewhere

enabled the California Hospital Association and the California Medical Association to play important and constructive roles during a most difficult period of adjustment in the Medi-Cal program. There is no doubt therefore that ready access to dependable facts has enabled the private sector in California to bring about substantial improvement in many voluntary and governmental health care programs.

It is against this background that the California Health Data Corporation was conceived and brought into being. It was founded less than a year ago jointly by the California Hospital Association and the California Medical Association. Its parents were therefore pioneers in the professional development of dependable health data and in use of the data to improve health care in both the private and public sector. It may be confidently expected that the genes of the parents will find far greater expression and far greater productivity in the accomplishments of the offspring, as it grows to maturity and takes its place in the California scene. Elsewhere in this issue may be found evidence that the pioneering trait has indeed been inherited.

Strong Stimuli

ADVANCES IN MEDICAL science often seem to create more problems than they solve. One such problem is how a busy practitioner is to keep up with these advances as they occur, and another is to determine the extent to which this is in fact accomplished. New knowledge comes to practicing physicians in many ways and from many sources. At times it even comes too soon, before it has been sufficiently checked or given adequate trial. This can be detrimental to patient care as well as to professional scholarship. More often the pressures of time and circumstance in busy practice become significant barriers to the study and review which is now necessary to stay abreast of new knowledge. No practicing physician wants to fall behind, but the pressures are often such that in the absence of a strong stimulus this may occur. Re-examination and re-certification of competence for professional practice are discussed elsewhere in this issue (see page 175). These would indeed be strong stimuli.



California Medical Association

Continuing Medical Education

Re-Examination and Re-Certification of Physicians

JUSTIN J. STEIN, M.D., *Los Angeles*

Member of the Scientific Board, California Medical Association

IN COMMENTING ON the obligation of state medical boards to evaluate clinical competence, character, physical and mental health, Breese¹ said: "Increasingly the public is demanding that these judgments not be made at just one point in time but often enough throughout the professional life of a licentiate to ensure the highest standards of care possible."

Whether we agree with this statement or not, there is a distinct possibility that unless sufficient voluntary efforts for continuing medical education are made by the practicing physician and by certifying and specialty organizations, governmental agencies will attempt to specify certain requirements which must be met for continued licensure.⁷

The major area of concern is the evaluation of the competence of the physician beyond the period of immediate postgraduate education. Adequate standards and safeguards exist now for the medical student, intern and residents. How can we determine the clinical competence of the physician who

has been out of school for a number of years and of the foreign graduate who completed his education in schools which may have different standards than those of our schools? The Educational Council for Foreign Medical School Graduates examination for foreign graduates is only a screening examination and is not intended for evaluation for licensure.

State medical board examinations given after graduation from medical school really do not determine the clinical competence of the physician (for at that time he has had limited clinical experience) but are mainly examinations for recall of information learned as a medical student. One might even question why physicians of approved medical schools in the United States who have just graduated have to be given an examination.

A committee called the Federation Licensing Examination Committee (FLEX)⁴ composed of

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⁷The author is a member and past president of the Board of Medical Examiners, State of California.

Reprint requests to: Department of Radiology, University of California, Center for the Health Sciences, Los Angeles 90024.

members from the boards of medical examiners of the various states has attempted, with the advice and help of many interested individuals and with the assistance of the National Board of Medical Examiners, to prepare an examination to test for clinical competence. This examination will be given in seven states in June and December 1968. Part III examinations of the National Board will be used for these two test periods. In the future, with additional experience, with acceptance by more state boards and with more uniformity in state licensing laws, an examination to test for clinical competence may become more generally accepted.

There is at present very little enthusiasm and desire by members of state medical boards to give periodic examinations for testing clinical competence as a requisite for re-certification of the license. For example, in 1966-67 there were 48,299 physicians who had valid California medical licenses. Of this number, 31,147 were residing in California, 16,058 in other states and 644 outside the United States. There would be numerous problems in preparing an examination of general type that would be applicable for all the licentiates, and in the giving of such an examination.

The general subject of re-examination and re-certification of licensed physicians has been repeatedly discussed by the Federation of State Medical Boards and by the National Board of Medical Examiners. No definite decisions have been made.⁵ Many believe that re-examination at various intervals may be desirable but no serious moves have been made in the direction of making such examinations a requirement for keeping a license.

The California State Board of Medical Examiners has always strived to protect the public as well as the medical profession by recommending changes in the Business and Professions Code regulating the practice of medicine in this state. For example, if a California licentiate loses his license for any of a number of reasons, such as gross incompetence, gross immorality or gross negligence, he must fulfill certain requirements before his license is restored. Section 2372.5 of the Code states: "The authority of the board to discipline the holder of a certificate by placing him on probation includes, but is not limited to the following: (a) Requiring the certificate holder to obtain additional medical training and to pass an examination upon the completion of the train-

ing. The examination may be written or oral, or both, and may be a practical or clinical examination, or both, at the option of the board. (b) Requiring the certificate holder to submit to a complete diagnostic examination by one or more physicians and surgeons appointed by the board. (c) Restricting or limiting the extent, scope, or type of practice of the certificate holder."²

These provisions in the law are excellent but they apply to the physician who has violated the provision of the Business and Professions Code. What about the physicians now in practice who make little or no effort to keep up with changes in medical knowledge and techniques? Re-examination is not required of them. More, a physician may discontinue practice for years and then return with license undisturbed. He is not required by law to have an examination to determine his clinical competence.

Somewhat related to periodic review of competence is a proposal made by the California Medical Association Committee on Continuing Medical Education and approved by the CMA Council: "That members of hospital medical staffs submit, on an annual basis, a listing of their activities in the field of continuing medical education as a requirement for hospital staff appointment." These listings would be used by the hospital medical staff for information only. Activities would include attendance at local, regional, or national scientific meetings, postgraduate courses, journal clubs, television conferences, grand rounds, or other organized continuing education programs. It is believed that one effect would be that each year in filling out his hospital appointment renewal application, the physician would have to review the efforts he has made for his continuing medical education. For those who have done little in this direction, the review might provide stimulus for a planned program. This is a worthy recommendation and it is hoped that all hospitals will place the question on their annual hospital appointment application forms. Eighty percent of the hospitals representing 53 percent of the total beds in the United States have no accredited program for interns and residents. In view of this, Schlicke⁶ has emphasized the necessity for the staffs of these hospitals to realize their responsibilities for continuing medical education.

I know of no specialty boards which plan to give examination for the purpose of re-certification at this time. The Academy of General Practice

makes certain requirements for continuing medical educations in order to maintain membership in the Academy. The American College of Physicians has planned an examination which may be taken voluntarily for the information of the candidate as to his medical competence.

Dillon³ recommended that medical organizations, such as the American College of Physicians, American College of Surgeons and others, require a certain amount of documented postgraduate work to maintain membership.

The half life of one's medical knowledge is about ten years. Without a planned program for continuing medical education it is impossible to keep abreast of the many changes and advances

being made in medicine. If physicians voluntarily assume this obligation for their continuing medical education, there will be no need for governmental intervention.

REFERENCES

1. Breese, M. W.: Continuing medical education and re-evaluation of the physician—responsibility of the individual, *Federation Bull.*, 4:369-374, Nov. 1967.
2. Compilation of laws relating to the practice of medicine and surgery, podiatry, dispensing opticians, physical therapy and psychology, State of California, Sacramento, Calif., Nov. 8, 1967.
3. Dillon, J. B.: A mechanism to assure continuing medical education, *Calif. Med.*, 106:235, Mar. 1967.
4. Merchant, F. T.: Testing for fitness to Practice, *Federation Bull.*, 55:118-129, April 1968.
5. Merchant, F. T.: Personal communication, May 20, 1968.
6. Schlicke, C. P.: Staff responsibility in a changing hospital environment, *Bull. Am. College Surg.*, 53:117, May-June 1968.
7. Stein, Justin J.: Continuing medical education and re-evaluation of the physician—Responsibility of the state medical boards, *Federation Bull.*, 54:354-369, Nov. 1967.

Immunization and The Registered Nurse

A Joint Statement on General Immunization and the Role of the Registered Nurse by the California Medical Association, the California Hospital Association, the California Nurses' Association and the California Conference of Local Health Officers.

BECAUSE OF THE possibility (even if remote) of individual reactions to biological agents used, and with the objective of protecting persons receiving general immunizing agents, and to protect the physician, the registered nurse, and any institution or agency participating, the California Medical Association, the California Nurses' Association, the California Hospital Association, and the California Conference of Local Health Officers acknowledges the right of registered nurses to administer biologicals as part of general immunization, but only if:

1. The nurse performs the necessary techniques in a clinic upon the order of a licensed doctor of medicine in attendance at the clinic site so long as injections are being given, and

2. The technique is to be performed within the framework of preparation and procedures for practice of the registered nurse, which have been established for the agency or institution by a committee composed of representatives of the agency or institution including doctors, registered nurses and administration. This framework of preparation, and of practice is to be reproduced in writing and a copy transmitted to the total medical and nursing staff, and

3. It is the jurisdiction of that committee in that agency or institution to:

- a) decide if the registered nurse may perform the technique and the conditions under which she may perform the technique.
- b) determine the preparation to be required of the registered nurse
- c) establish inservice teaching to be required
- d) delineate the immunizing agents that nurses may administer, and
- e) set up medical guiding principles to govern the treatment of possible anaphylactic reactions

June 15, 1968

❧ In Memoriam ❧

ADAMS, BURTON W., Oakland. Died 30 June 1968 in Oakland from injuries suffered in an automobile accident, aged 62. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Adams was a member of the Alameda-Contra Costa Medical Association.



BARNES, MYRON C., Ontario. Died 1 June 1968 at Ontario in a private plane crash, aged 64. Graduate of the College of Medical Evangelists, 1940. Licensed in California in 1940. Doctor Barnes was a member of the San Bernardino County Medical Society.



BOBBITT, ARTHUR NEWTON, Pasadena. Died 3 April 1968 of coronary artery thrombosis, aged 82. Graduate of Vanderbilt University School of Medicine, Nashville, 1909. Licensed in California in 1915. Doctor Bobbitt was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



BROWN, MARY HESS, Los Angeles. Died 7 June 1968 in Los Angeles of arteriosclerotic heart disease, aged 91. Graduate of Cornell University Medical College, New York City, 1900. Licensed in California in 1901. Doctor Brown was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



BROWN, SEYMOUR MILTON, Palm Springs. Died 3 April 1968 of intracranial hemorrhage, aged 54. Graduate of Long Island College of Medicine, Brooklyn, 1938. Licensed in California in 1952. Doctor Brown was a member of the Riverside County Medical Association.



BUSH, JOSEPH, Newport Beach. Died 2 July 1968 in Newport Beach of coronary occlusion due to arteriosclerotic heart disease, aged 41. Graduate of State University of Iowa College of Medicine, Iowa City, 1954. Licensed in California in 1959. Doctor Bush was a member of the Orange County Medical Association.



CECIL, LEE M., San Rafael. Died 10 June 1968 in Kentfield, aged 42. Graduate of University of Michigan Medical School, Ann Arbor, 1949. Licensed in California in 1954. Doctor Cecil was a member of the Marin Medical Society.

CHARLTON, CECIL FLOYD, Pasadena. Died 14 March 1968 of hypertensive arteriosclerotic heart disease, aged 81. Graduate of Rush Medical College, Chicago, 1910. Licensed in California in 1915. Doctor Charlton was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



CHARNOCK, DONALD AUSTIN, Los Angeles. Died 16 July 1968 in Los Angeles, aged 74. Graduate of Harvard Medical School, Boston, Massachusetts, 1925. Licensed in California in 1926. Doctor Charnock was a member of the Los Angeles County Medical Association.



CHRISTIENSEN, CLIFFORD MAURICE, Oakland. Died 3 July 1968 in Oakland, aged 45. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in California in 1951. Doctor Christiansen was a member of the Alameda-Contra Costa Medical Association.



DEITZ, KATHLEEN MURPHY, San Francisco. Died 19 June 1968 in San Francisco, aged 59. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1935. Licensed in California in 1935. Doctor Deitz was a member of the San Francisco Medical Society.



DORNAN, DALLAS DWIGHT, Laguna. Died 21 June 1968 in Fullerton, aged 48. Graduate of University of Kansas School of Medicine, Lawrence-Kansas City, 1945. Licensed in California in 1952. Doctor Dornan was a member of the Orange County Medical Association.



GELFAND, ALEX JACOB, West Covina. Died 15 June 1968 in Los Angeles of carcinoma of the thyroid, aged 49. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1950. Licensed in California in 1950. M.D. degree from California College of Medicine, 1962. Doctor Gelfand was a member of the Los Angeles County Medical Association.



HOULIHAN, ROBERT G., San Mateo. Died 1 July 1968 in San Mateo of heart disease, aged 49. Graduate of Northwestern University Medical School, Chicago, Illinois, 1943. Licensed in California in 1946. Doctor Houlihan was a member of the San Mateo County Medical Society.

KATZ, ROBERT A., Los Angeles. Died 23 June 1968 in Los Angeles, aged 59. Graduate of the University of Minnesota Medical School, Minneapolis, 1939. Licensed in California in 1947. Doctor Katz was a member of the Los Angeles County Medical Association.



KINSELL, LAURANCE WILKIE, Oakland. Died 9 July 1968 in Oakland, aged 60. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1932. Licensed in California in 1943. Doctor Kinsell was a member of the Alameda-Contra Costa Medical Association.



KOEPSSELL, ARTHUR A. H., Sacramento. Died 3 July 1968 in Sacramento, aged 63. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in California in 1944. Doctor Koepsell was a member of the Sacramento County Medical Society.



KRAJESKI, ROMUALD J., San Francisco. Died 10 June 1968 in San Francisco of heart disease, aged 57. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1938. Licensed in California in 1946. Doctor Krajewski was a member of the San Francisco Medical Society.



LAHMANN, ALBERT HENRY, Mequon, Wis. Died 5 Jan. 1968 in Milwaukee of heart disease, aged 65. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1926. Licensed in California in 1947. Doctor Lahmann was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



LIPTON, MORRIS LESTER, Antioch. Died 27 June 1968 in Antioch of myocardial infarction, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Lipton was a member of the Alameda-Contra Costa Medical Association.



MANKIN, HAROLD, Berkeley. Died 10 June 1968 in Berkeley of arteriosclerotic heart disease, aged 49. Graduate of Harvard Medical School, Boston, Massachusetts, 1942. Licensed in California in 1951. Doctor Mankin was a member of the Alameda-Contra Costa Medical Association.



MARNELL, FRANK S., San Diego. Died 29 June 1968, aged 85. Graduate of Washington University School of Medicine, St. Louis, Mo., 1904. Licensed in California in 1919. Doctor Marnell was a member of the San Diego County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.



MASON, PERCY WILLIAM, Los Angeles. Died 7 March 1968, aged 66. Graduate of University of Toronto Faculty of Medicine, Ontario, Canada, 1926. Licensed in California in 1951. Doctor Mason was a member of the Los Angeles County Medical Association.

MATLOCK, P. WILSON, Fresno. Died 24 February 1968 near Watsonville from accidental drowning, aged 50. Graduate of Western Reserve University School of Medicine, Cleveland, Ohio, 1948. Licensed in California in 1949. Doctor Matlock was a member of the Fresno County Medical Society.



McMILLAN, G. S., Indio. Died 6 June 1968 in Indio, aged 59. Graduate of University of Nebraska College of Medicine, Omaha, 1936. Licensed in California in 1943. Doctor McMillan was a member of the Riverside County Medical Association.



MOORE, WILLIAM HOMER, SR., Bakersfield. Died 19 June 1968, aged 75. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1919. Licensed in California in 1919. Doctor Moore was a retired member of the Kern County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



NASH, ACATIUS N., Los Angeles. Died 12 June 1968 in Los Angeles, aged 59. Graduate of Université de Genève Faculté Médecine, Switzerland, 1933. Licensed in California in 1942. Doctor Nash was a member of the Los Angeles County Medical Association.



ROBBINS, GEORGE WILLIAM DEWEY, Los Angeles. Died 29 June 1968 in Los Angeles of myocardial infarction, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1926. Licensed in California in 1926. M.D. degree from California College of Medicine, 1962. Doctor Robbins was a member of the Los Angeles County Medical Association.



SCHULTE, JOHN W., San Francisco. Died 7 June 1968 in Idaho of heart disease, aged 54. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1940. Licensed in California in 1940. Doctor Schulte was a member of the San Francisco Medical Society.



SLAVICK, EDWARD FRANK, Arcadia. Died 29 March 1968 in Los Angeles of hypostatic bronchopneumonia, aged 78. Graduate of University of Illinois College of Medicine, Chicago, 1913. Licensed in California in 1925. Doctor Slavick was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



STAFFORD, WALTER G., Whittier. Died 18 March 1968 in Pico Rivera, aged 55. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1946. Licensed in California in 1946. M.D. degree from California College of Medicine, 1962. Doctor Stafford was a member of the Forty First Medical Society.



VARNEY, J. HOWARD, Bakersfield. Died 17 February 1968, aged 57. Graduate of University of Oregon Medical School, Portland, 1942. Licensed in California in 1942. Doctor Varney was a member of the Kern County Medical Society.

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.

Director, State Department of Public Health

Lapses of Consciousness Are Reportable

ARE YOU, AS A physician, a contributor to highway accidents? Certain kinds of medical conditions are a major factor and it is the physician's responsibility for reporting patients with such conditions to the Department of Motor Vehicles, although this has long been a subject of controversy and confusion. Recent studies by the Department of Public Health show that drivers with conditions such as epilepsy, diabetes, cardiovascular disease, alcoholism, and mental illness have about twice as many crashes per unit of driving exposure as do healthy drivers of similar age,^{1,2} and that problem drinking and alcoholism are involved in about a third of all highway fatalities.^{3,4}

The primary responsibility for reporting of potentially hazardous medical conditions to the Department of Motor Vehicles rests with the driver himself. He must indicate if such conditions are present each time he applies for or renews a driver license. In addition, since 1939, state law has required reporting by physicians of patients with epilepsy or similar conditions. The physician reports the patient to his local health department, which in turn reports through the State Department of Public Health to the Department of Motor Vehicles. The fact that the physician has been the source of reporting is kept from the patient. Neglecting to report can result in successful suit against the physician, as demonstrated by a recent case in New Jersey where a patient with epilepsy who was not reported crashed during a seizure.

In 1966, following a change in the state law, the state regulations were modified to read as follows:

"2572. Disorders Characterized by Lapses of Consciousness. As required in Section 410 of the Health and Safety Code, the definition as to what shall constitute a reportable case of a disorder characterized by lapses of consciousness shall be as follows:

" 'Any person aged 14 years or older who during the preceding three years, has experienced on one or more occasions, either a lapse of consciousness

or an episode of marked confusion, caused by any conditions which may bring about recurrent lapses, including momentary lapses of consciousness or episodes of marked confusion, shall be considered to have a disorder characterized by lapses of consciousness and shall be reportable.

" 'This definition includes, but is not limited to persons subject to lapses of consciousness or episodes of marked confusion resulting from neurological disorders, senility, diabetes mellitus, cardiovascular disease, alcoholism or excessive use of alcohol sufficient to bring about blackouts (retrograde amnesia for their activities while drinking).' "

The physician who follows the law — and his own conscience — will be contributing materially to the safety of life and limb of us all, in helping to identify drivers with chronic medical conditions.

The important changes in this law and these regulations are:

1. The reporting law no longer is limited to epilepsy but includes many conditions, and especially problem drinking, which may be hazardous to driving.

2. Only persons age 14 or over are reportable.

3. Reporting is required only of persons with recent episodes of altered consciousness which are likely to be recurrent.

When a new report is received by the Department of Motor Vehicles the patient is interviewed by a driver improvement analyst and further information is obtained from the physician only after a written release has been obtained from the patient. Licenses are revoked initially for fewer than half the drivers interviewed, and many of these have their licenses returned after their conditions improve. For more difficult cases, several local medical societies have established committees to assist the Department of Motor Vehicles in evaluating the medical ability of individuals to drive. The final decision about the driving privilege rests upon medical and other information and must be made by the Department of Motor Vehicles.

1. Waller, J. A.: Chronic medical conditions and traffic safety—Review of the California experience, *New Eng. J. Med.*, 273:1413-1420, 1965.

2. Waller, J. A.: Cardiovascular disease, aging, and traffic accidents, *J. Chron. Dis.*, 20:615, 620, 1967.

3. Waller, J. A., and Turkel, H. W.: Alcoholism among driver and pedestrian fatalities, *New Eng. J. Med.*, 275:532, 1966.

4. Waller, J. A.: Identification of problem drinking among drunken drivers, *JAMA*, 200:114-120, 1967.

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Dr. Alfred Coodley, associate clinical professor of psychiatry at UCLA Medical Center, has been elected president of the Southern California Psychoanalytic Society.

SACRAMENTO

The American Association for Automotive Medicine will conduct its annual meeting in Sacramento October 17 and 18 at the Sacramento Inn. Dr. George Snively, a member of the California Medical Association Committee on Automotive and Traffic Safety, is president of this group.

* * *

Dr. Edward Rudin has been appointed coordinator of planning for the newly designated Sutter Hospital Community Mental Health Center. Dr. Rudin is director of Sutter Hospitals Diagnostic and Treatment Center, which provides psychiatric services for emotionally disturbed children and adolescents, and out-patient hearing and speech services for children and adults. The facility whose planning Dr. Rudin will direct is encompassed in the United States Public Health Service plans for a mental health center to serve each geographical area with a population of 75,000 to 200,000.

* * *

The multi-discipline approach to therapy of metastatic cancer is the theme of the Fourth Annual Cancer Symposium to be held in Sacramento the afternoon and evening of 17 September. The symposium is sponsored annually by the American Cancer Society in cooperation with the Sacramento County Medical Society and this year the University of California Medical School at Davis has become a co-sponsor. The symposium, which is to be held in the Sacramento Inn, will deal with aspects in the treatment of metastatic cancer of the breast, colon and ovary from the viewpoint of four

disciplines, the pathologist, the surgical oncologist, the radiotherapist and the medical oncologist.

SANTA CLARA

Dr. Robert J. Glaser, vice president for medical affairs and dean of the Stanford University School of Medicine, has been named acting president of the university, effective 1 September, upon the retirement of president J. E. Wallace Sterling.

Dr. Glaser will be assisted in his new assignment by vice president and provost Richard W. Lyman, who will continue as chief academic officer under the president, as well as by other members of the president's staff.

Dr. Thomas A. Gonda, associate dean of the School of Medicine, has been appointed acting director of Stanford University Hospital.

Dr. John L. Wilson, formerly dean of the Faculties of Medical Sciences at the American University of Beirut, has been appointed an associate dean and director of Regional Medical Programs at Stanford University School of Medicine. He will also serve as professor of surgery. As director of the Regional Programs, he will plan the groundwork for cooperative medical programs related to heart disease, cancer and stroke in Stanford's assigned region, which embraces the counties of Calaveras, Mariposa, Merced, Monterey, San Benito, San Joaquin, San Mateo, Santa Clara, Santa Cruz, Stanislaus and Tuolumne.

* * *

A three-year grant of \$225,824 to the Stanford University School of Medicine from the John A. Hartford Foundation, Inc., for support of continuation of a search for the cause and cure of psoriasis was announced recently. Psoriasis research in the Department of Dermatology at Stanford has been supported by the Foundation since 1959.

GENERAL

Mrs. William R. Flood of Pleasant Hill and Mrs. Lyle F. Murphy of Long Beach were placed in leading positions in the Woman's Auxiliary to the American Medical Association at the auxiliary's recent annual meeting in San Francisco. Mrs. Murphy was elected western regional vice president of the organization and Mrs. Flood was named legislation chairman. Both are former presidents of the Woman's Auxiliary to the California Medical Association.

The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 48 of the Advertising Section.

FATIGUE FRACTURES—A Clinical Study—James M. Morris, M.D., Assistant Professor of Orthopaedic Surgery; Research Associate, Biomechanics Laboratory, University of California School of Medicine, San Francisco, Calif., and Loren D. Blickenstaff, M.D., Major, U.S. Army Medical Corps. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1967. 217 pages, \$15.50.

This clinical monograph calls attention to a relatively unexplored area of orthopedic interest and summarizes the authors' experience with seven hundred cases of fatigue fracture of the bones of the pelvis, leg and foot observed between 1963 and 1965 in military recruits at the Fort Ord Infantry Training Center. The material is divided into three introductory chapters covering general considerations and some interesting speculation on etiology, and seven chapters describing symptoms, signs and x-ray findings in lesions of the lower extremity. One hundred and forty-five pages or roughly two-thirds of the book are devoted to x-ray photographs, some of which, as the author notes, are of variable quality but which overall give to even the casual reader a wide exposure to the types of fracture encountered.

The authors stress the frequency with which the diagnosis may be missed because of lack of familiarity with the syndrome and urge that the diagnosis be made frequently by inference from clinical findings alone in the early stages when radiographs are often negative. The spontaneous resolution of stress fracture with only the simplest forms of supportive treatment is described but the authors take pains to except fatigue fracture of the femoral neck where delayed diagnosis can lead to disruption of the fragments, damage to blood supply and the catastrophe of non-union. Almost all patients were fresh recruits of previous sedentary occupation and ninety-nine percent were Caucasian. The clinical syndrome was encountered in almost all the bones of the pelvis and the lower extremity.

There is much to recommend this modest volume; the authors have presented what must be considered the definitive work on a clinical condition which is not generally encountered outside of military dispensaries, and have suggested that its occurrence in civilian life is often mis-diagnosed or missed entirely with occasional disastrous results. They are perhaps too enthusiastic in applying the condition too readily to the aches and pains of growing children and "shin splints" and strains of the adult, but appear to be correct in stressing its occurrence as a precursor to prolonged disability in fractures of the femoral neck where early recognition alone may prevent crippling.

The volume, whose bibliography contains two hundred and thirty-seven references covering one hundred years,

deserves to be included in all comprehensive orthopedic libraries, and may be considered essential in military medical installations.

EDWARD H. WILSON, M.D.

* * *

KINESIOLOGY AND APPLIED ANATOMY — The Science of Human Movement — 3rd Edition — Philip J. Rasch, Ph.D., F.A.C.S.M., Chief, Physiology Division, Naval Medical Field Research Laboratory, Camp Lejeune, North Carolina; and Roger K. Burke, Ph.D., F.A.C.S.M., Professor of Physical Education, Occidental College, Los Angeles, California. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1967. 488 pages, \$8.50.

In this third edition the authors have undertaken the formidable task of reviewing both classic findings and recent advances in the understanding of the basic functions of the human neuromusculoskeletal system. They have attempted to apply this information to physical or athletic training and to the treatment of certain musculoskeletal disorders.

The first part of the book is devoted to the composition, development, and function of the skeleton and its joints, the skeletal muscle system, and the nervous system. Recent basic research in these areas, includes studies in electron microscopy, cellular physiology, and electromyography, has been included. Two chapters are devoted to the nervous system; spinal reflexes, kinesthetic and servomotor control, conditioning reflexes, and motor learning are discussed.

A second section considers the human body as a machine and outlines the principles of mechanics and kinematics which apply to the musculoskeletal system. The concepts of dynamic mechanics, inertia, force, kinetics, lever systems, work, strength, and power are discussed as they apply to the musculoskeletal system.

The third part of the book is a moderately detailed review of movements of the major and minor joints of the upper and lower limbs and movements and stabilization of the spinal column and thorax. The anatomy and function of the musculature involved in these movements are presented in some detail. Implications for athletic training are included with the discussion of each joint or area in this section of the book.

In the final section, basic physiologic and structural aspects of the musculoskeletal system are considered as they apply to the kinesiology of posture, walking, running, and jumping. A separate chapter on the kinesiological principles in sports and games deals with such factors as application of kinesiology to warm-up, starting positions, terminal positions, strength, follow-through, stabilization, summation of forces, angular momentum, and falling.

A final chapter discusses kinesiology in the activities of daily living, such as lifting, moving weights, sitting and relaxing, kneeling, stair climbing, arrangement of working space, and avoidance of industrial fatigue.

Obviously, a single volume of 488 pages cannot cover completely such a vast subject as the basic physiology, anatomy, and kinesiology of the human musculoskeletal system, with therapeutic and practical applications. The authors, however, have expended a great deal of time and effort to bring together, in readable form, pertinent information, including references to the literature and numerous (234) illustrations which have been carefully chosen to document and emphasize the contents of the volume. An adequate index is available to those who may wish to pursue certain subjects in greater detail.

Although written primarily as a textbook, this volume is a valuable addition to the working libraries of those individuals engaged in physical therapy and the training of athletes. It is also an excellent review and reference manual for members of the medical profession who are engaged in the study and treatment of disorders of the musculoskeletal system.

It has been a pleasure to review this contribution to the medical literature.

JAMES M. MORRIS, M.D.

* * *

THE MADNESS IN SPORTS — Arnold Beisser, M.D., Director, Center for Training in Community Psychiatry, Los Angeles, State Department of Mental Hygiene; and Clinical Professor, Psychiatry and Human Behavior, University of California, California College of Medicine, Appleton-Century-Crofts, Division of Meredith Publishing Company, 440 Park Avenue South, New York, N.Y. (10016), 1967. 241 pages, \$4.95.

The author clearly points up "the madness" in sports by recounting psychiatric case studies. He describes the complex and involved motivation behind successful athletes, and enumerates some of the social pressures of our society which assist in producing such compelling drives in the youngsters. The material is new, stimulating and thought provoking for all physicians, not only those concerned with the psychological and physical problems of athletes.

The author's summation of our undue preoccupation with sports and masculinity, I think, is valid, and his criticism should be heeded. Each reader shall judge for himself the Freudian relationship to competitive sporting events. Could not hereditary traits in man account for a competitive drive similar to that exhibited by all young animals whose play frequently leads to training for subsequent competition and survival?

CHARLES G. HUTTER, M.D.

* * *

HUMAN TRANSPLANTATION — Edited by Felix T. Rapaport, M.D., Associate Professor of Surgery; Head, Transplantation and Immunology Division, Department of Surgery; New York University Medical Center; Director of Research, Institute of Reconstructive Plastic Surgery, New York University Medical Center; Visiting Surgeon, Bellevue Hospital, New York, N.Y.; and Jean Dausset, M.D., Prof. Ag., Faculté de Médecine, Université de Paris; Directeur d'Immunohématologie, Centre Georges Hayem, Paris; Institut de Recherches de la Faculté de Médecine, Université de Paris; Biologiste des Hôpitaux de la Ville de Paris. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 728 pages, \$38.50.

This is a beautifully illustrated compendium of present experience in organ transplantation. There is some discussion of the genetic basis for and against homotransplantation of organs, and there is the proper amount of space given to considerations of moral and ethical problems. Experts in the transplantation of almost every organ system have written clearly and succinctly in their own areas of interests. Like all books relating to the fast

developing field of organ transplantation, it is already outdated by recent contributions, particularly in the area of heart transplantation. I believe it is an excellent book for reference and library use, but the individual physician will probably gain more information from the current medical literature.

NORMAN E. SHUMWAY, M.D.

* * *

INFECTIOUS DISEASES OF CHILDREN—Fourth Edition—Saul Krugman, M.D., Professor and Chairman, Department of Pediatrics, New York University School of Medicine, New York, N.Y.; Director of Pediatrics, Bellevue Hospital Center, New York, N.Y.; Director of Pediatrics, University Hospital, New York, N.Y.; and Robert Ward, M.D., Professor and Chairman, Department of Pediatrics, University of Southern California School of Medicine, Los Angeles, Calif.; Physician-in-Chief, Childrens Hospital, Los Angeles, Calif. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 428 pages, \$16.50.

This book can be read only with wistful wonder that the authors have compressed such an amazing amount of authoritative material into a succinct volume. Three previous editions are updated and considerably improved upon. Almost every detail regarding both common and less common infectious diseases which the clinician may encounter has been covered in a most admirable manner: etiology, immunology, clinical manifestations, prevention and treatment.

There is an adequate bibliography which extends well into 1968, practically up to yesterday or the day before. Even more to the point are the authors' comments on the validity and importance of the literature and they have not hesitated to express their own opinions on many disputatious matters. One might disagree with a very few statements—but only at his own peril. There are numerous capsule case histories which illustrate and enliven the general discussion.

This book is sufficiently compact to be a source of ready reference but it is sufficiently authoritative and detailed that one will rarely need to go further for information. Anyone with a special interest in the subject matter will find it hard to avoid reading this book from cover to cover.

EDWARD B. SHAW, M.D.

* * *

DIAGNOSTIC LABORATORY HEMATOLOGY — Fourth Edition, Revised and Enlarged—George E. Cartwright, M.D., Professor of Medicine, College of Medicine, University of Utah, Salt Lake City, Utah. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 441 pages, \$10.00.

This is the outstanding manual for techniques employed in routine clinical hematology laboratories. The author has selected preferred methods rather than presenting many possible alternatives. This edition follows the previous one by five years, and has been extensively rewritten to encompass the major new developments in this rapidly growing field.

It is difficult to find fault with the author's choice of methods or clarity of exposition. It is unfortunate, however, that the section on red cell antibodies in acquired hemolytic anemia is largely adapted from publications of Dacie, and techniques thus follow those generally used in England. For example, the directions for the antiglobulin test are not appropriate for the antiglobulin reagents generally available in this country.

Nonetheless this small volume receives our highest recommendation. It is suitable for physicians and for technologists. A copy belongs in every hematology laboratory and library.

HERBERT A. PERKINS, M.D.

Preoperative Radiation in the Treatment of Cancer

JUSTIN J. STEIN, M.D., *Los Angeles*

■ *In the treatment of advanced cancer of the hypopharynx, preoperative radiation therapy has proven to be of value for the prevention of recurrences in the operative area following radical neck dissection for cancer of the head and neck. Also it has been of value in the planned combined therapy of certain patients with lung, bladder, breast, esophagus, bone, endometrial and rectal cancers.*

Preoperative radiation therapy should be advantageous in patients who have malignant disease where the possibility exists for the cancer cells to be disseminated during the surgical procedure.

IN RECENT YEARS there has been increasing interest in the use of preoperative radiation therapy. The impression has been that if radiation is effective when given postoperatively, then the possibilities are that before operation, when the blood supply to the involved area has not been compromised and there has been no trauma, it may offer even greater benefits.

The availability of megavoltage equipment, permitting precise dosimetry, skin sparing, improved depth dose, less scattering of the beam and less differential absorption of the radiation in the various tissues of the body, has contributed to the effectiveness of such therapy. The training of the radiation therapist is constantly improving, and more physicians are specializing in the therapeutic

application of ionizing radiation with due concern for the complete medical care of the patient.

Clinical Basis for Use

It is not always possible by known diagnostic methods to determine the full extent of the malignant disease. Cancer cells may already have spread beyond the operative field without any clinical evidence to indicate the extent of the disease.

Because of infiltration of cancer cells into the tissues locally, or as a result of the proximity to certain vital organs, complete removal of the cancer may not be possible.

In the presence of local edema and/or infection there may be a question whether the tumor is operable, as for example, in certain cases of breast cancer or carcinoma of the recto-sigmoid colon.

Cancer cells may remain in the operative area following the completion of the operation, or may have been disseminated during the surgical procedure.

From the Department of Radiology, University of California, Los Angeles, Center for the Health Sciences.

Presented at the Dallas Southern Clinical Society Meeting, Dallas, 18 March 1968.

Submitted 11 April 1968.

Reprint requests to: Department of Radiology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles 90024.

Problem of Preoperative Irradiation

Among the problems associated with preoperative radiation therapy are the following:

- What is the optimum preoperative tumor dose, and the period of time over which it should be given?
- Should the operation immediately follow completion of the preoperative radiation therapy, and, if not, then what is the optimum delay?
- To what extent may preoperative radiation therapy cause undesirable delay in operation?
- What are the possibilities for an increase in morbidity, or complications or delay in wound healing, or in mortality, when preoperative radiation therapy is given?
- How many viable cancer cells, capable of reproducing to produce recurrent metastatic disease, will remain in the operative area?

Advantages

Following are some of the advantages of preoperative radiation therapy:

- When there is a question of operability or when there is a reasonable chance that it will not be possible to completely remove the tumor, preoperative radiation therapy may be of particular value.
- The incidence of recurrences in the operative area, when cancer cells remain following the operation, may be prevented or reduced.
- The viability and the ability to reproduce, of those cancer cells which may have been disseminated incidental to the trauma of the surgical procedure, will be diminished.
- An area considerably larger than that intended for surgical excision can be included in the radiation field.

Effects

The direct effect of radiation upon the cancer cells is instantaneous and there may be ancillary advantages:

- The cancer cells may be either destroyed or rendered incapable of reproduction.
- The host's immune mechanism may be stimulated.
- Beneficial effects may be exerted on the cancer bed lymphatics, the blood supply, and the supporting tissues.
- Since they have a better blood supply, are younger and are dividing at a more rapid rate,

small nests of cancer cells and those located in the peripheral portions of the cancer are more radio-sensitive than those in the central mass or core. Any necrotic or anoxic cells in the central portion are more likely to be completely removed by surgical operation.

If a cancer is quite small, freely movable, and one which can readily be removed with a wide margin of surrounding tissue, the use of preoperative radiation therapy is probably not indicated. If metastasis has already occurred, then preoperative radiation therapy is certainly not justified.

Data Based on Animal Studies

From experiments on mice, DeSault⁵ and Kasenter presented evidence that irradiated tumors, even when not controlled by this therapy, grow more slowly than untreated tumors.

Feder⁶ and associates attempted to answer certain questions as to the possible justification for a small dose of preoperative radiation, the importance of fractionation and the optimum period of delay between the time of radiation and resection. They expressed belief that sufficient scientific evidence has been presented in the literature for the justification of a small dose of preoperative radiation. They have also demonstrated that preoperative radiation in relatively small doses significantly reduced the transplantability of a C3H rhabdomyosarcoma to a C3H mouse. Laboratory investigations have been reported indicating that the growth potential of a tumor can be reduced by small doses of preoperative radiation. Feder⁶ and coworkers believe that if preoperative radiation at higher dose levels is to be used clinically, the radiation therapist must still determine the optimum degree of fractionation in his effort to enhance the therapeutic ratio. At low dose levels preoperative radiation may be more effective if very little fractionation is employed.

Hoye⁷ and Smith, in experiments with mice, attempted to reduce the number of tumor cells disseminated at operation, by treating the primary intact tumor 24 hours preoperatively with radiation or systemic TSPA in dosages that would be insufficient to stop the growth or cause regression of the primary tumor. The growth of tumor which was disseminated intravascularly, intramuscularly or into an axillary wound from the *in vivo* treated primary tumor was decreased by more than 90 percent.

Inch and McCredie⁸ reported experiments in

which preoperative administration of a single dose of x-radiation (2,000 rads) to the carcinosarcoma 256 Walker mouse tumor, 24 hours before excision, caused a significant reduction in the number of local recurrences. They considered preoperative more effective than postoperative radiation because the tumor cells were still in situ before operation and the blood supply was still intact. For clinical application they recommended giving the small dose of radiation over a short period immediately preceding operation.

Suit¹⁸ and Schiavone described an experiment to estimate the extent of transfer of cells out of the hypoxic compartment following a single radiation dose, or two doses, to a mouse mammary carcinoma with an intertreatment interval of five days. The results led them to believe that there is strong evidence that in some solid tumors the degree of the hypoxic fraction is not constant but is subject to change and does decrease during the course of the fractionated radiation.

In an experimental study using mice, reported by Vermund¹⁹ and associates, inhibition of tumor growth was found to increase linearly with increasing doses to a maximum at about 3,000R. Larger doses do not produce a greater effect. When the tumor was transplanted to the brain, where a sparsity of connective tissue exists, no tumor bed effect was noted. The radiation-induced changes that give rise to the tumor bed effect remained present for at least nine months.

Powers¹⁶ and coworkers reviewed a series of 214 patients who were operated on after radiation therapy and found no demonstration of an optimal dose of radiation, or of time interval between radiation and operation, to permit complete and adequate wound healing with minimum delay. Studies in animals revealed that small doses of radiation cause relatively little delay, whereas doses in the order of 4,000 rads caused considerable delay in healing in some of the animals.

Quantitative extrapolation of these and other animal data to human therapy should obviously not be attempted, but some qualitative trends may perhaps be suggested.

Clinical Usefulness

Preoperative radiation therapy has proven to be of value in the treatment of patients with advanced cancer of the laryngopharynx, for the prevention of recurrences in the operative field following radical neck dissection for patients with head and

neck cancer, and in planned combined therapy of patients with lung, bladder, breast, uterus, bone, kidney and rectal cancers.

A "curative" course of radiation therapy has been advocated by some radiation therapists, with operation to follow in approximately six to eight weeks in order that the major effect from the ionizing radiation on both the cancer cells and the tumor bed would have taken place.

After a "curative" course of radiation therapy (approximately 6,000 rads given in approximately six weeks for epidermoid carcinoma) has been given, there may be an increase in postoperative complications, delay in wound healing, increased technical difficulties at operation, greater morbidity, and possibly some increase in mortality. Buschke² and Galante believe that high cancerocidal radiation doses can be given preoperatively when longer protraction and megavoltage radiation therapy are used and that the vasculoconnective tissues can be preserved. They gave preoperative radiation therapy to ten patients with cancer of the head and neck, using one million volt x-rays (3.2mm Pb. h.v.1.) and between 6,000 and 8,000 R (skin) in 32 to 39 days, for a minimal tumor dose of 4,100 to 6,500 R through one field. Operation was done in from one to five and one-half months after completion of the therapy. There were no surgical complications beyond those which one would anticipate when no preoperative radiation therapy was given.

In Carcinoma of the Lung

My own experience has been that if preoperative tumor doses in excess of 4,000 rads in four weeks are given, the possibilities for increased morbidity, mortality and operative technical problems are increased. When tumor doses of 5,000 rads in five weeks were given preoperatively for the treatment of lung carcinoma, using x-rays from the 6 Mev linear accelerator, there was a definite increase in morbidity and mortality. After the initial experience of treating carcinoma of the lung preoperatively with this technique in 20 patients, the tumor dose was reduced to 4,000 rads in four weeks, and there was a decrease in morbidity and complications.

Bloedorn¹ expressed belief that the use of preoperative radiation may be effective in the treatment of bronchogenic carcinoma provided that a definite program of policies and techniques of treatment can be developed and that close coopera-

tion exists between all specialists concerned in the combined program.

Mallams¹¹ and coworkers, reporting on the results of a seven-year study utilizing preoperative radiation therapy followed by operation in four weeks for clinically diagnosed apparently localized bronchogenic carcinoma of the superior sulcus type, expressed an opinion that this may be the treatment of choice. Of 28 patients treated, two were alive after more than six years, and five of nine patients who were suitable for four-year evaluation were alive and well. Thirty-three percent of 24 patients were alive and well at the end of two years. The tumor dose given preoperatively varied from 3,000 to 3,500 rads given in 15 treatments during a period of 19 days. Mallams¹¹ held that increasing the radiation dose will result in more complications without increasing the survival rate. Paulson,¹⁵ in 1967, said that of 34 patients with superior pulmonary sulcus carcinomas who completed combined therapy from 1956 through 1965, 12 had a five-year survival. There were two operative deaths and a minimum of complications. He was of the opinion that complete sterilization by radiation therapy is not necessary and may even be harmful because of the effect upon the normal tissue cells and the interference with the normal tissue reparative processes.

In Carcinoma of Esophagus

Nakayama¹⁴ said he believed preoperative radiation should be given as an adjunct to operation, for the treatment of carcinoma of the upper and midthoracic portions of the esophagus. He advocated a three-stage operative procedure, the first stage being gastrostomy and removal of the lymph nodes of the celiac axis and paracardia. One week after the first surgical stage a total dose of radiation varying from 2,000 to 2,500 rads, given in four to five sessions of 500 rads each, (Cobalt 60) is given. Several days after the completion of irradiation, a total thoracic esophagectomy and cervical esophagostomy are performed as the second stage. A third stage antethoracic esophagogastrotomy is usually performed six months after the first stage.

In patients with cancer of the upper and mid-thoracic esophagus treated by radiation and operation, the four-year survival rate was 31.8 percent, compared with 15.4 percent in patients treated by resection only. There was very little change in morbidity or mortality.

Clifton³ and coworkers reported on 20 patients with esophageal cancer who had received a full course of preoperative radiation therapy. In 11 of these patients resection was carried out and it was found that the cancers had regressed considerably, in some cases had disappeared.

Watson,²¹ using only external radiation therapy, obtained good results in the treatment of cancer of the upper two-thirds of the esophagus. Radiation therapy was begun in 16 and completed in 14 of 21 consecutive cases of cancer in this location. Four of the irradiated patients lived five or more years and three were still alive at the time of the report.

In Laryngopharyngeal Cancer

Lederman¹⁰ expressed the opinion that most patients with early, localized laryngopharyngeal cancer can be given a preliminary course of radiation therapy, using "curative" doses, with hope for cure. For the more advanced cases he preferred preoperative radiation therapy when operation is indicated. He believed that with the blood supply intact there is a greater opportunity to shrink the cancer, to destroy or render the cancer cells less likely to proliferate and cause metastasis or recurrence at the site of the wound.

The effect of radiation on the supporting tissues and on the blood supply of the tumor bed are important. It is possible that the resistance may be affected but this is difficult to determine. There is an increase in the collagen and the hyalinization of the connective tissue. The blood supply is reduced because of the changes in the endothelium. The reduction in the lymph and blood supply can act as a deterrent to the spread of tumor cells.

Silverstone¹⁷ and coworkers said they believed radical operation would offer a better prognosis for patients with advanced cancer of the laryngopharynx if the peripheral portion of the tumor could be reduced in extent so that the operative procedure would be the equivalent of an operation for an early lesion instead of an advanced lesion. They recommended preoperative radiation therapy in order to destroy or render non-reproductive the peripheral portion of the tumor, with operation following in about three weeks, before the recovery of growth activity of the remaining cancer cells. A tumor dose of 5,500 rads in about five weeks, a rest interval of three to six weeks, and then radical operation was recommended. Megavoltage therapy (Cobalt 60) was used. They en-

countered no technical difficulties and the wounds, without complications from infection or fistula information, all healed completely. Twenty-one patients with advanced cancer of the laryngopharynx, all stage III, completed a course of combined therapy and 16 had survived for periods from five to fifty-one months at the time of report. These investigators have continued the combined program on the basis of the favorable results obtained.

In Breast Cancer

There are not yet enough clinical data available to assess the value of preoperative radiation therapy in the treatment of operable breast cancer. If there are no problems, concerning operability (the tumor is small and there is no skin involvement and no metastasis) preoperative radiation therapy probably should not be done; it should be reserved for patients with large tumor mass, involvement of the skin and on the borderline of operability.^{13,14}

In Carcinoma of the Bladder

Because cystectomy alone for bladder carcinoma has not produced sufficiently favorable five-year survival rates, DeWeerd⁴ and Colby have studied the effects of combining the procedure with preoperative radiation therapy. One group of patients with infiltrating transitional or squamous cell carcinoma were given preoperative radiation to the bladder region, using either external Cobalt 60 or 6 Mev x-rays. The total tumor dose was about 4,800 rads given in two sessions, each session consisting of 2,400 rads delivered in a period of 12 to 14 days with a rest interval of three weeks. Total or segmental cystectomy and partial lymphadenectomy were carried out six weeks after the second irradiation. No residual intact cancer cells could be found in nine surgical specimens. There was no increase in postoperative complications, morbidity or mortality.

A second group of patients with infiltrating bladder tumors received a total tumor dose of from 1,800 to 2,400 rads given to the bladder region during three consecutive days at the rate of 600 rads daily, and then total or segmental cystectomy and partial pelvic lymphadenectomy immediately afterward. There was no increase in morbidity, mortality or complications.

Using radiation therapy (tumor dose of 3,500 rads given at the rate of 200 rads tumor dose daily to the bladder region), plus 5-fluorouracil (5-FU),

and then operation, Kaufman and Stein⁹ treated 71 patients who had bladder tumors of various orders. Seven of nine patients who had recalcitrant Stage A tumors and eight of fifteen patients with Stage B1 lesions were tumor-free; and the resected specimens of bladders from seven of twenty patients with Stage B2 and C tumors were tumor-free. Five patients with Stage D1 or D2 tumors had lived more than two years at the time of the report, and three had lived reasonably comfortably for more than four years. This study is continuing.

In Cancer of the Head and Neck

Early diagnosis or recognition of malignant lesions involving the head and neck while in a localized stage is most important, for a high proportion can be cured by operation, by radiation therapy or by a combination of the two. Yet in a surprising number of cases malignant disease in this region is in advanced stage when first diagnosed. This is probably due in part to inadequate routine examinations of the head and neck region, by neglecting biopsy of suspicious lesions, and sometimes by the patient's delay in consulting a physician. It should be noted in this regard that painful lesions are sometimes treated with antibiotics and if the symptoms improve, considerable time may elapse before biopsy is done and definitive treatment begun.

After the diagnosis is made and the extent of the disease determined the first physician who makes the decision as to the method of therapy bears the responsibility for the outcome. If the therapy selected is inadequate or not appropriate, subsequent therapy will be much less effective.

The primary lesions may initially produce few if any symptoms, and the first indication of disease may be the presence of metastatic disease in the nodes of the neck. For example, a high proportion of patients with primary cancers of the nasopharynx have metastatic disease in the neck when first seen. If an enlarged lymph node suspected of containing metastatic disease is present when the patient is first seen, the head and neck regions should be thoroughly examined (repeatedly if necessary) before the node is removed for biopsy. Not to do so may delay treatment of the primary cancer, making subsequent radical neck dissection more difficult and increasing the likelihood that the operative area will be "seeded" with tumor cells.

Millburn¹² and Hendrickson evaluated all of the 409 patients with primary disease in the oral

pharyngeal or laryngeal areas (squamous cell carcinoma) who had radical neck dissection at Presbyterian-St. Luke's Hospital. There were 163 patients in the group who had microscopically positive lymph nodes in the neck. Radical neck dissection alone was performed in 112 patients, and 28 of them (25 percent) were free of disease at the end of two years. Preoperative radiation therapy and planned radical neck dissection were carried out in 51 patients, and 46 of them (90.2 percent) were free of disease in the neck at the end of two years. The same surgeons were involved in both groups of patients. When there was recurrence, the interval between operation and the re-appearance of cancer was essentially the same: for operation only it was eight months; with combined therapy, five months. None of the patients with initially positive lymph nodes who survived free of disease for two years ever had recurrence in the treated area.

Strong²⁰ and coworkers reported the results of a cooperative controlled study of preoperative x-ray therapy as an adjunct to radical neck dissection. Only patients with histologically confirmed epidermoid or squamous cell cancer, primary in the head and neck region, and who had no previous operative or radiation therapy to the neck other than needle aspiration biopsy or tracheostomy, were included. The most common primary tumor sites in this group were tongue, floor of the mouth and extrinsic or supraglottic larynx. The technique of preoperative radiation was to use a single lateral port extending from the mastoid area to the chin, mandible and clavicle, with 400 R given daily for five days for a total dosage of 2,000 R. Operation was performed the day of the final treatment or as soon afterward as feasible. Megavoltage therapy was used. Patients who were born on even-numbered birthdays received no preoperative radiation to the neck and constituted the control series. Among patients with positive nodes, 30.9 percent of the treated group and 50 percent of the controls had recurrence in the neck. In the group with

negative nodes, none of the treated group and 7.8 percent of the controls had recurrence in the neck. Strong pointed out that the incidence of local recurrence of metastatic cancer in the neck following radical neck dissection in the treatment of cervical lymph node metastasis from primary head and neck cancers usually varied from 26 to 29.8 percent.

REFERENCES

1. Bloedorn, F. G., Chapter 8 on Lung, page 412, in: *Textbook of Radiotherapy*. Edited by Gilbert H. Fletcher, M.D., Lea & Febiger, Philadelphia, 1966.
2. Buschke, F., and Galante, M.: Radical preoperative roentgen therapy in primarily inoperable advanced cancers of the head and neck, *Radiology*, 73:845-848, Dec. 1959.
3. Clifton, E. E., Goodner, J. T., and Bronstein, E.: Preoperative irradiation for cancer of the esophagus, *Cancer*, 13:37-45, Jan.-Feb. 1960.
4. DeWeerd, J. H., and Colby, M. Y., Jr.: Bladder carcinoma, *JAMA*, 199:145-147, 9 Jan. 1967.
5. DeSaut, L. A., and Kasenter, A. G., Jr.: "Cure" or "Control" of tumors, *Radiology*, 86:444-446, March 1966.
6. Feder, B. H., Blair, P. B., and Close, P.: Fractionation in preoperative irradiation, *Radiology*, 84:447-451, March 1965.
7. Hoye, R. C., and Smith, R. R.: The effectiveness of small amounts of preoperative irradiation in preventing the growth of tumor cells disseminated at surgery, An experimental study, *Cancer*, 14:284-295, March-April 1961.
8. Inch, W. R., and McCredie, J. A.: Effect of a small dose of x-radiation on local recurrence of tumors in rats and mice, *Cancer*, 16:595-598, May 1963.
9. Kaufman, J. J., and Stein, Justin J.: Chemotherapy and radiation as surgical adjuvants in the treatment of carcinoma of the bladder. To be published.
10. Lederman, M.: Role of irradiation in the treatment of cancer of the hypopharynx, postcricoid and cervical esophagus, Paper presented at the International Workshop on Cancer of the Head and Neck, New York City, 10 to 14 May 1965, pp. 347-356, published by Butterworths, Washington, 1967.
11. Mallams, J. T., Paulson, D. L., Collier, R. E., and Shaw, R. R.: Presurgical irradiation in bronchogenic carcinoma, superior sulcus type, *Radiology*, 82:1050-1054, June 1964.
12. Millburn, L. F., and Hendrickson, F. R.: Initial treatment of neck metastases from squamous cell cancer, *Radiology*, 89:123-126, July 1967.
13. Moss, W. T.: The Breast, Chapter 10, pages 217-243, *In Therapeutic Radiology*. Edited by W. T. Moss, 2nd Ed., C. V. Mosby Co., St. Louis, 1965.
14. Nakayama, K., Orihata, H., and Yamaguchi, K.: Surgical treatment combined with preoperative concentrated irradiation for esophageal cancer, *Cancer*, 20:778-788, May 1967.
15. Paulson, D. L.: Discussion of paper by Tildon, T. T., and Hughes, R. K.: Complications from preoperative irradiation therapy for lung cancer, *Ann. Thoracic Surg.*, 3:324-325, April 1967.
16. Powers, W. E., Ogura, J. H., and Palmer, L. A.: Radiation therapy and wound healing delay, *Radiology*, 89:112-115, July 1967.
17. Silverstone, S. M., Goldman, J. L., and Rosin, H. D.: Combined therapy, irradiation and surgery for advanced cancer of the laryngopharynx, *Am. J. Roentgenol. Rad. Therapy and Nu. Med.*, 90:1023-1031, Nov. 1963.
18. Suit, H. D., and Schiavone, J. V.: Effect of a single dose of radiation, *Radiology*, 90:325-328, Feb. 1968.
19. Summers, W. C., Clifton, K. H., and Vermund, H.: A study of the indirect actions of radiation on transplantable tumors, *Radiology*, 82:691-703, April 1964.
20. Strong, E. W., Henschke, V. K., Nickson, J. J., Frazell, E. L., Tollefson, H. R., and Hilaris, B. S.: Preoperative x-ray therapy as an adjunct to radical neck dissection, *Cancer*, 19:1509-1516, Nov. 1966.
21. Watson, T. A.: Radiation treatment of cancer of the esophagus, *Surg., Gynec. Obstet.*, 117:346-354, Sept. 1963.

Drug Abuse

Recommendations for California Treatment and Research Facilities

FREDERICK M. MEYERS, M.D., AND DAVID E. SMITH, M.D., *San Francisco*

■ *The California Legislature has directed the Regents of the University of California to collect and act as an information exchange on research and services relating to drug abuse, and to provide advice with respect to fields in which research is needed.*

The current report, prepared under that directive, outlines the method by which data on drug abuse research and treatment facilities will be collected, and how this data will be prepared so that appropriate recommendations can be made to the state legislature.

This initial report also outlines areas of immediate concern in the area of drug abuse for the benefit of the state legislature. These areas include current state policies which interfere with investigators competing for federal research funds; pharmacological misclassification of various agents of drug abuse (including marijuana, cocaine and mescaline); lack of awareness of the major adolescent drug abuse problem in California, namely that associated with methamphetamine abuse; the inconsistent and destructive effects of current Nalline clinic programs, and legal restraints which interfere with the proper treatment of drug abusers by physicians trained in treating such patients.

THE CALIFORNIA LEGISLATURE, by the addition of Section 210 to the Health and Safety Code in 1967, directed the Regents of the University of California to “. . . collect, and act as an information exchange for, information on research and service projects completed or in progress relating to drug abuse . . .” and to provide advice with

respect to the areas in which research is needed. The authorized activity, called the “Drug Abuse Information Project,” is now being carried out at the San Francisco Campus of the University of California under our direction.

This report is submitted pursuant to the requirements of the legislation.

Plans for the Project

1. *Organization.* The regents of the university have allocated funds for the operation of the Infor-

From the Pharmacology Laboratory, University of California Medical Center, San Francisco.

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Reprint requests to: Pharmacology Laboratory, University of California Medical Center, San Francisco 94122 (Dr. Meyers).

mation Project for the balance of this fiscal year, and funds have been requested for fiscal 1968-69. The project was activated in December 1967. The address of the project is: Department of Pharmacology, University of California Medical Center, San Francisco, California 94122, and the telephone number is (415) 666-1951.

Dr. Frederick H. Meyers, professor of pharmacology, and Dr. David E. Smith, clinical instructor in pharmacology and physician to the Drug Abuse Screening Unit of the San Francisco General Hospital, will devote part-time to the project. Fortunately, a person able to help with substantive as well as clerical matters has been employed.

2. *Operation.* Information will be solicited from each individual or agency identifiable as associated with research or service in the area of drug abuse. These are startlingly large in number. Interested individuals may be working in medicine, pharmacology, chemistry or the social or behavioral sciences, or be involved in police, correctional or rehabilitative efforts.

Directors of research of several of the large state agencies have already been actively cooperative. A questionnaire will be distributed to individual research and service efforts and community studies.

The data will be used to carry out the intention of the legislature:

(a) By providing to any interested investigator information about projects related to his own. Data submitted by investigators not associated with any agency of the state will be regarded as privileged; that is, individuals carrying out related or even highly similar projects will be identified but actual research plans will not be disclosed.

(b) By the collection and systematic analysis of reported drug abuse, arrive at conclusions which scattered, individual or institutional data cannot reveal;

(c) By encouraging the more consistent and perhaps more uniform reporting of results of treatment programs and studies of incidence;

(d) By the preparation of a report embodying our interpretation of the collected data and the suggestions of the contributors.

Reasons for Preliminary Report

Since authorization and funds for this project have only recently become available, this report obviously is not based on data collected in the manner described above. Nevertheless, a fraction

of the research and service programs existing in the state are known to the directors of this project, either through scientific publications or through personal contact.

Two important rationalizations or goals justify preparation of a report at this time.

1. *Provision of information to agencies and individuals studying drug abuse.* This or a similar document will be used to inform those concerned about the function assigned this project. The discussions of some areas of public policy below will certainly stimulate the submission of suggestions and additions along with the data about research or service activities in progress. Such reaction should help us to move toward presentation of a consensus in some areas and to present most of the divergent views in others.

2. *Information about immediate legislative problems.* The introduction to the drug-using groups of drugs not presently regulated and the content of some interim committee hearings suggest that consideration of certain problems will occur during the present regular session. This report presumes to present certain definitions as well as to provide the suggestions requested by the enabling legislation.

Some Definitions and a Survey of the Problem

The definitions and concepts outlined below will, initially at least, underlie the organization of the data collected.

The key idea is that there is not a single problem of drug abuse but a variety of problems involving different agents and with different patterns of drug use. These different problems involve entirely different degrees of danger to the drug user and to society. The concept of the multiplicity of problems explains the frequent reference in this report, and in the work of others, to the consistency or inconsistency of present regulations and legal definitions. The term narcotics, for example, as now defined in the Health and Safety Code, encompasses a diverse group of drugs that would not be classified into a single category by the scientific community.

1. *Factors in the Development of Drug Abuse.* The properties of the drug are of obvious importance in the development of a pattern of drug misuse. Yet, the use of a particular drug is not uniformly distributed throughout our society. Studies of the epidemiology of drug abuse show

an irregular distribution of the problem and suggest that some groups and certain individuals are more susceptible than others. In order to understand the development of the several different patterns of drug misuse, one must consider three factors or influences.

(a) **Drug Factors.** The pharmacological effects of a drug are of great importance in determining its potential for misuse. However, drugs that are commonly misused are from different pharmacologic classes, and indeed the effects of one group may be diametrically opposite to those of another group of misused agents. For each drug or drug class the hazard to the user and to society must be evaluated, and this evaluation will be quite different for different drugs. The several drug classes are listed in the following section.

(b) **Individual (Psychological) Factors.** Since, however, drug misuse does not reflect simply the availability of the drug, additional factors must be operating to determine individual liability. Alcohol, the most commonly misused drug, is freely available to all members of our culture, but our patterns of alcohol use vary widely. Some individuals reject it; some use it temperately and socially; some use it episodically to excess; and a tragically large number develop a compulsive pattern of misuse which destroys their own and other lives.

(c) **Group (Sociologic) Factors.** Individuals form attitudes and react as members of groups. The attitudes and problems of their group condition their use of drugs. Heroin misuse, now declining in incidence, was predominantly a disease or crime of the ghettos of large cities. Other ethnic or religious groups in our society are statistically unusually susceptible or resistant to the development of chronic alcoholism.

The attitudes of the dominant group in our culture are reflected in the laws, such as those that are permissive of alcohol, tobacco, and other social or recreational drugs which are actually quite harmful. There are, of course, sub-groups within our pluralistic society which feel that the prohibitions against their social drugs are arbitrary and unjustified by the actions of the drug. This conflict between groups is the basis for the current criticism of the laws regulating the use of marijuana.

2. **Drug Classes.** The many individual drugs subject to misuse can be placed in a few groups or classes of drugs. The following classification introduces only one area of controversy, and this is clearly identified.

(a) **Sedatives.** This class of drugs might also be labeled sedative-hypnotic or depressants. Included are alcohol, barbiturates and similar sleeping pills, the hydrocarbons found in glue and elsewhere, and marijuana. With increasing doses, each of these agents first causes sedation and relief from anxiety. Larger doses lead to a stage of disinhibition, with disturbance of psychomotor performance and judgment. Still larger doses may produce coma and even death. The hazard of these drugs to individuals and to society through the precipitation of irresponsible acts is not uncommon.

The classification of marijuana in this category is controversial. Many students with experience and competence in this area feel that the classification of marijuana must await further research. In our judgment, the confusion is due in large part to the low potency of the "grass" commonly available today. Studies in other cultures, for example throughout the Muslim world and India where potent preparations of the nearly pure resin are used, appear to establish the same sequence of effect as described above, and to further establish the potential for compulsive misuse of the potent preparation by some individuals. It must be acknowledged that the brief duration of action and low potency of available marijuana preparations, and its freedom from the nutritional side effects of alcohol, do indeed suggest a lesser hazard in the use of marijuana. In any case, its present legal classification as a narcotic comparable to heroin appears to be unsupported by any authority outside of the enforcement area.

(b) **Narcotics or Opiates.** Heroin, morphine or other alkaloids of opium, and various synthetics are dangerous because of the great potential for compulsive misuse. Nevertheless, the danger lies not so much in the drug effect itself, as in the associated criminal activity generated by the expense of the habit. The user is depressed by the drug and not led to anti-social behavior during the action of the drug.

(c) **Major Stimulants.** For a number of reasons, methamphetamine (speed, crystal) has replaced heroin as the drug most likely to be injected compulsively. The paranoid state engendered by large and repeated doses is of major social concern. The oldest drug of this class of pure stimulants is cocaine; which is legally classified as a narcotic. *Methamphetamine* (Methedrine, Desoxin) or *dextroamphetamine* (Benzedrine, Dexedrine) are also abused by oral administration

and more than an occasional case has followed therapeutic administration. Of the drugs encountered by the exploring or experimenting young person today, methamphetamine appears to us to be by far the most threatening.

(d) *Minor Stimulants.* Minor central nervous system stimulants, such as nicotine in cigarettes and caffeine in coffee, are listed here for two purposes. First, to establish that there are drugs accepted as social or recreational agents. Second, to suggest that an understanding of the problem and the treatment of compulsive drug misuse is perhaps best developed by studying similar compulsive acts in ourselves. The compulsive use of cigarettes may be an act senselessly repeated without great satisfaction. The same statement describes the compulsive use of illegal drugs.

(e) *Hallucinogens.* LSD is used to cause distortion in perception and may, in large doses, result in the hallucinatory, paranoid state referred to as an effect of methamphetamine. In fact, at least two substances (STP, MDA) chemically related to methamphetamine, have recently been used in lieu of LSD. With rare exception the use of LSD is episodic since at least three days must elapse between doses if the state of disordered perception is to be experienced.

3. *Patterns of use.* The episodic use of marijuana or alcohol and the ritualistic use of LSD represent a lesser evil than the development of the compulsive use of a drug such as methamphetamine, alcohol or heroin. Yet laws which punish possession for use make no distinction between the pattern of intended use. The State of California has already moved to treat compulsive drug misuse as an illness rather than a crime, although existing laws are inconsistent and limiting of this progress.

Possible Areas of Immediate Concern

Several areas of immediate need or concern are now discussed under the general headings of research, treatment and service, and education. They are presented at this time in part because they may be of immediate interest, and in part to solicit reactions preparatory to our subsequent reports.

Research

This report will provide "advice with respect to the areas in which research is needed" as requested by AB 1399, with the caution that the fragments are based on consultation with only a small fraction of interested investigators.

1. *Distribution of Research Effort.* The difficulties involved in increasing the amount of research in this area supported by state funds are apparent. Neither can the amount of federal funds allocated to the area of drug abuse be predicted at this time. The National Institute of Mental Health (NIMH) has recently been reorganized and now includes a Center for Studies of Narcotic and Drug Abuse. (This Center has announced its intention of encouraging research on marijuana, but for reasons mentioned below, California investigators will compete poorly for these funds.) The distribution or direction of the research efforts within the state could be altered, whether the total amount is increased or not, by reallocating funds to emphasize current problems and attitudes.

(a) *Previous Emphasis.* Research that is supported or encouraged by the state unduly emphasizes enforcement needs and punitive attitudes. The continued emphasis on heroin does not reflect the changing pattern of drug misuse. The emphasis on diagnosis, that is detection, of drug use, and on surveillance of individuals has led to disproportionate emphasis on the chemical approach by scientists.

(b) *Suggested Approach.* With the exception of badly needed studies on marijuana, information about drugs is adequate to permit treatment or abatement efforts. Compulsive drug use should be regarded as symptomatic of some underlying difficulty and emphasis placed upon the psychiatric and social factors involved. Control and treatment measures undertaken by any agency, but especially the large state-supported rehabilitative efforts, should be evaluated more exactly in order to permit expansion of successful techniques at the expense of less effective measures. Since large numbers of young people are now involved in experimentation with nominally illegal drugs, local groups and agencies should be encouraged to carry out research in the sense of incidence studies and determination of the fate of young drug users.

2. *Restriction of Research on Marijuana.* A recent addition to the Health and Safety Code (11655) has had the effect of inhibiting research on marijuana at the very period when it needed most to be encouraged. Practically speaking, only schools of medicine can possess marijuana for investigative purposes and even in this situation a research proposal must be approved by a technically untrained enforcement officers. Individuals who have used large amounts of heroin and metham-

phetamine in their laboratory and clinical research without untoward incidents find marijuana difficult to obtain. For example, a private laboratory awarded a \$70,000.00 annual contract by the NIMH is legally forbidden to carry out that part of the contract involving the chemical study of marijuana. No restraint beyond the requirements of careful accounting for supplies of the drug would appear necessary. At the very least, the review of the scientific merits of the project should be carried out by a group of the investigators' scientific peers rather than by a single administrator.

3. *Evaluation of "Nalline" Programs.* The injection of a narcotic antagonist to determine whether probationers are using a narcotic is still widely used in California. This test will only detect the use of "narcotics" in the medical sense; that is, heroin but not methamphetamine or marijuana. The antagonist is not completely free of narcotic effects and a fraction of the subjects experience a heroin-like effect. If the limitations of the test and the change in the pattern of drug use are not recognized, the test may be applied to users of drugs other than heroin. In at least one county marijuana users may be paroled to the Nalline program, a frightening error but legal within the definitions established by the special legislation afforded the Nalline test.

An evaluation of the Nalline programs and the imposition of some slight restrictions appear justified at this time.

Service and Treatment

During the past 47 years, federal and state laws have had the effect of isolating or alienating the physician and the therapist from the drug user. Interest in and willingness to work with problems of drug abuse are increasing as more and more children of the middle class become involved. Development of closer relations between counselors from the "straight" world and members of the drug-using sub-culture can be accelerated by legislative action.

1. *Revision of Narcotic and Dangerous Drug Laws.* The narcotic and dangerous drug laws have evolved until they now include what can only be called pharmacologic inconsistencies and even absurdities. The Narcotic Law properly defines heroin as a narcotic but defines marijuana, a drug with entirely different properties and patterns of use, in the same way and assigns equally

severe penalties for its possession and sale. Cocaine, a central nervous stimulant, is also defined as a narcotic, but methamphetamine, a far more widely used stimulant, is defined as a dangerous drug. Mescaline is a stimulant and hallucinogen, the use of which is actually legal for one group within the state. Yet it is defined as a narcotic, while the more commonly available LSD and the more or less equivalent tryptamine derivatives are classed as dangerous drugs.

(a) *Penalties for Possession of Marijuana.* Suggestions that marijuana be "legalized" have been misleading to the extent that they suggest that a total absence of regulation of marijuana would be desirable. However, a very immediate need is to bring the penalties for the possession or use of marijuana into concordance with the dangers inherent in the drug, rather than maintaining the position that it is equivalent in its hazards to heroin. A quite startling number of young people have had experience with marijuana and recognize the inaccuracy of such claims. The present laws threaten to further alienate an entire generation and to destroy respect for all laws regulating the use of drugs and, indeed, for all drug information provided by established agencies.

(b) *Possession as a Crime.* The Congress has assigned the control of those drugs included in the California Dangerous Drug Law to a Bureau of Drug Abuse Control in the Food and Drug Administration. Possession for use of these drugs is not defined as a crime, but penalties for possession for sale or for importation remain. If our goal is cure or abatement rather than punishment, such legislation entails no loss and makes the provision of treatment much simpler.

(c) *Reporting and Prohibition of Treatment of Addicts.* The Narcotic Laws currently forbid treatment of the "narcotic addict" outside of specified institutional settings and require that an addict be reported by name. "Addict" is not defined by the law, but "narcotic" includes marijuana as well as heroin. These restrictions are a source of concern to people working with drug users and have been one of the devices isolating the users from medical care. The parallel federal law has not been upheld in the courts but the "Warning on Narcotic Law" included in the directory distributed by the State Board of Medical Examiners warns in bold type, "Attention is called to the prohibition of treatment of ambulation narcotic addicts." In practice, enforcement agencies have modified the law but such

modification would appear to be a legislative function.

2. *Establishment of Treatment Centers and Programs.* The feeling that drug abuse is purely a criminal matter appears to be less tenaciously held as the size of the problem increases and the general citizenry sees their own children involved. If the alternate medical or therapeutic approach is to have any success it must be supported beyond the present level, even if such support is obtained at the expense of enforcement efforts. At this time, adequate government support is not available. For example, the State Department of Public Health is not authorized to maintain a section on problems of drug abuse, and city-supported facilities in San Francisco have actually been decreased recently.

In addition to the support now provided through the Department of Mental Hygiene or the California Youth Authority, the state might consider a subsidy to stimulate local activity. The activities of the Bureau of Alcoholism of the State Department of Public Health and the matching programs that it administers provide a model that could be modified or expanded.

In passing, it should be emphasized that all of the problems discussed thus far are quantitatively much less important than alcoholism. Research and treatment in that area should certainly not be curtailed because of the greater emotional impact of the illegal drugs. The problems of alcohol abuse and the abuse of other drugs are so similar that a single Bureau of Alcoholism and Drug Abuse, rather than separate offices, should be considered by every agency.

(a) Which problems require treatment? Different drugs and different patterns of use require different treatment facilities. The variety of facilities, some within the user's community and some in centralized hospitals, which are needed relate directly to the variety of therapeutic problems.

(1) Acute drug reactions. Acute intoxication by stimulants or depressants and adverse reactions to LSD or other hallucinogens are usually treated in a public hospital. If the detoxification unit is separately organized and a physician familiar with drug users is available, the acute treatment may possibly require less time but, more importantly, a larger fraction of the patients can be induced to accept after-care.

(2) Compulsive drug users. The treatment of heroin and methamphetamine use is extremely dif-

ficult. The legislature has already reduced somewhat the restriction on treatment. Continued encouragement of state hospitals and voluntary agencies is essential. In addition, "Half-way Houses" and other community psychiatric facilities function in this area.

(3) Problems unrelated to drug abuse. Very few young drug users solicit help for the problem of their drug use. They do request help for psychiatric problems that antedate their drug use. If drug use is largely symptomatic, expansion of general facilities will have an impact on drug use.

(4) Individuals who acknowledge no illness. For the foreseeable future there will continue to be a large group of young drug users who regard themselves as neither criminal nor ill. The principal drug used by this group is marijuana. A smaller group uses LSD, with the nominal goal of reaching self-understanding or with a philosophic or religious motivation.

It is easy to overemphasize the threat of this group since they—our children—are so virulently anti-middle class. The problems of raising our children cannot, however, be reduced to a matter of pharmacology nor can we incarcerate a quarter of the juvenile population. Any psychiatric remedy for the situation must be applied to the parents as well as to the youth. Treatment is important, but education will probably be far more important for this group and their parents.

Education

The severely punitive approach to problems of drug abuse followed for the past few years has obviously not prevented the increased use of marijuana, LSD and other drugs. The rigorous laws have separated the drug-using patient from the therapist and from dependable sources of information. Distrust of enforcement agencies and of most general (if emotionally based) public attitudes drives the young user to the drug-using subculture for information.

If information from an established source is inaccurate for one drug known to young persons, they will subsequently reject more accurate data about another drug. Again, marijuana is the drug of central importance because, if our information about it is judged to be palpably inaccurate, our warnings about LSD, methamphetamine, and others, are also rejected. Self-experimentation with drugs is thereby encouraged since it is judged to be the only dependable source of information.

If our goal is control and prevention rather than retribution, only widespread education and counseling offer real hope. Effectiveness of such efforts will be somewhat limited by the extent to which drug use is symptomatic of underlying social and individual problems, but authoritative information about drugs and drug laws would probably reduce self-experimentation with drugs. Several studies (notably the one conducted by the Juvenile Justice Commission of San Mateo County) emphasize that the teenager's own ethical system and the fear of *physical* consequences are far greater deterrents to drug use than parental attitudes or legal consequences.

Several school districts are attempting to modernize their instruction and to provide counseling in addition to the required hours of instruction. In most communities, however, assistance from experienced workers from one of the treatment facilities described above will be required.

The effort of the State Department of Education to provide the badly needed manual of information for teachers and others has been disappointing. The book was prepared by two inexperienced gentlewomen who apparently were more concerned with "public acceptance" than with the technical advice of their advisory committee.

CORRECTION

In the article, "Re-Examination and Re-Certification of Physicians" by Justin J. Stein, M.D., in the August issue of CALIFORNIA MEDICINE, reference 6 (page 177) indicated that the work referred to was originally published in the *Bulletin of the American College of Surgeons*. It was not. It was reprinted in the *Bulletin of the American College of Surgeons*, with permission, from *Northwest Medicine*, 66:715-717, August, 1967, where it originated.

Coronary Care Units

The Status in California

ELLIOTT M. STEIN, M.D., JO ANN WRAY, B.S., WILBUR C. BERRY, M.D., AND
NEMAT O. BORHANI, M.D., *Berkeley*

■ *In order to determine the status of Coronary Care Unit activity in California hospitals, especially as it pertains to nurse training, a survey was conducted by the California State Department of Public Health. More than 95 percent of hospitals that were questioned responded. Only one-third of the hospitals reported they neither had a unit nor plans to build one. All units in operation were either directed by an individual medical director or by a Coronary Care Unit Committee.*

The survey indicated that in some hospitals with operational units, nurses were not permitted to perform life-saving resuscitative procedures. All operational units reported in-service education programs of some type. Many hospitals indicated they would like to have Coronary Care Unit training programs to which they could send nurses. The reasons why nurses may not perform important resuscitative procedures are discussed as well as the need for Coronary Care Unit training programs for both physicians and nurses in California.

DEATH FROM ACUTE myocardial infarction among patients in hospital is often due to sudden and unanticipated arrhythmia which, if detected early enough, could be arrested in most cases. Recent advances in constant monitoring systems and improvements in electronic equipment for the treatment of heretofore fatal complications of acute myocardial infarction have led to the establishment of coronary care units (CCU) where patients are kept under constant observation during the acute phase of the disease. Unexpected complications are thus detected early enough for appropriate treatment.

There has been great interest in the establish-

ment of coronary care units in many hospitals in California. Rapid development of these units created the need for specially trained nurses. This demand for trained and experienced personnel has, in turn, focussed attention on the need for specific and specialized training programs.

In an attempt to determine the extent of this need and type of training required, the California Heart Association, California Medical Association, California Nurses' Association, California Hospital Association and the California State Department of Public Health sponsored a special survey which was carried out by the Department of Public Health in June 1967.* Highlights of this survey are presented in this communication.

Submitted 5 Jan. 1968.

Reprint requests to: California State Department of Public Health, Bureau of Chronic Diseases, 2151 Berkeley Way, Berkeley 94704 (Dr. Berry).

*The complete report of the survey is available from the California State Department of Public Health, Bureau of Chronic Diseases, 2151 Berkeley Way, Berkeley 94704.

Methods and Material

The sponsoring agencies developed a questionnaire which was mailed to directors of nursing in all hospitals with 50 or more acute general beds. Data obtained from the questionnaires were tabulated and analyzed by the staff of the Bureau of Chronic Diseases. For the purpose of the survey the following definition of a coronary care unit was developed.

A Coronary Care Unit is defined as a specialized unit staffed by specially trained nurses and equipped with electronic monitoring equipment and resuscitative devices for the care of patients with acute or suspected myocardial infarction or acute disorders of cardiac rhythm.

Results

Questionnaires were mailed to 304 hospitals; 290 responded, a response rate of 95.4 percent. A total of 70 hospitals (23 percent) reported having coronary care units in operation; an additional 87 (28.6 percent) had definite plans to establish coronary care units. Twenty-eight hospitals (9.2 percent) expected to have units but their plans were indefinite at the time of the survey; 103 hospitals (33.9 percent) had no plans to establish such units. (See Table 1).

Eighty percent of the units in operation reported having medical directors (Table 2). The remaining 20 percent were directed by coronary care unit committees. Among those units expected to open in the future, 77 percent reportedly will have medical directors; 15 percent will be directed by a coronary care unit committee. Ninety-seven percent of the directors of existing units were either cardiologists or internists. Of hospitals with existing and operational units, 88.6 percent have coronary care unit committees independent of whether or not there is a medical director; among planned units, 91 percent indicated they will have such committees.

Table 3 shows a summary of the number of hospitals which permit their coronary care unit nurses to perform resuscitative procedures. In all existing operational units, nurses were reported to perform cardiopulmonary resuscitation; in 80 percent nurses were permitted to carry out defibrillation, 83 percent to begin either internal or external pacing, and 40 percent to administer the

TABLE 1.—Operational Status of Coronary Care Units in Surveyed Hospitals

Coronary Care Unit Status	Number	Percent
All Hospitals	304	100.0
CCU Operational	70	23.0
Definite Plans for CCU	87	28.6
Indefinite Plans for CCU	28	9.2
No Plans for CCU	103	33.9
No Plans Reported	2	0.7
No Response to Survey	14	4.6

TABLE 2.—CCU Medical Direction and CCU Committees by Operational Status of Coronary Care Units

CCU Medical Direction and CCU Committees	Operational CCU		Planned CCU	
	Number	Percent	Number	Percent
Unit Director	70	100.0	87	100.0
Have Medical Director	56	80.0	67	77.0
Directed by CCU Committee	14	20.0	13	14.9
Undecided	7	8.0
CCU Committee	70	100.0	87	100.0
Have CCU Committee	62	88.6	79	90.8
No CCU Committee	8	11.4	4	4.6
Undecided	4	4.6

TABLE 3.—Hospitals that Permit CCU Nurses to Perform Emergency Procedures by Operational Status of Coronary Care Units

Emergency Procedures and Response	Operational CCU		Planned CCU	
	Number	Percent	Number	Percent
Cardiopulmonary				
Resuscitation	70	100.0	87	100.0
Yes	70	100.0	82	94.3
No
Not Reported or Undecided	5	5.7
Defibrillation	70	100.0	87	100.0
Yes	56	80.0	63	72.4
No	13	18.6	2	2.3
Not Reported or Undecided	1	1.4	22	25.3
Pacing—External or Internal	70	100.0	87	100.0
Yes	58	82.9	66	75.9
No	11	15.7	2	2.3
Not Reported or Undecided	1	1.4	19	21.8
Emergency Drug Administration	70	100.0	87	100.0
Yes	28	40.0	46	52.9
No	38	54.3	7	8.0
Not Reported or Undecided	4	5.7	34	39.1

drugs urgently needed in cardiac standstill and ventricular fibrillation.

Hospitals with units in operation were questioned as to continuing education courses provided for coronary care unit nurses. All hospitals with full-time CCU nurses reported ongoing in-service

TABLE 4.—Continuing Education for CCU Nurses in Hospitals with Operational Coronary Care Units

Continuing Education	Number	Percent
Continuing Education in CCU		
Techniques	70	100.0
Yes	64	91.4
No	2	2.9
Not Reported	4	5.7
Frequency of Continuing Education		
Courses	70	100.0
None	2	2.9
Continuous (not otherwise specified)	3	4.3
Each Week	32	45.7
Each Month	11	15.7
Less than Each Month	11	15.7
Not Reported	11	15.7

TABLE 5.—Preferred Length of Training Course for CCU Nurses at a Specialized Center, by Operational Status of Coronary Care Units

Length of Training	Operational CCU		Planned CCU	
	Number	Percent	Number	Percent
All Hospitals	70	100.0	87	100.0
No Training	11	15.7	3	3.4
Two Weeks	20	28.6	23	26.4
Four Weeks	15	21.4	31	35.6
Six Weeks	8	11.4	6	6.9
Not Reported	16	22.9	24	27.6

programs; nearly 70 percent have sessions at least once each month and almost half have weekly training sessions (Table 4).

In an attempt to determine what kind of training was needed and would be utilized by hospitals with coronary care units, hospital administrators and nursing directors were asked how many nurses they would send to a specialized center for training, and for how long. Only 16 percent of hospitals with ongoing units and 3.4 percent of hospitals with definite plans for such units reported they would not send their nurses for training (Table 5). Nearly all that expressed a desire to send nurses to an outside medical center indicated willingness to give the nurses time off with pay.

The exact number of nurses in need of training is not known, since about one third of the hospitals did not indicate the number of nurses they might send. However, the survey did show a critical need for training programs: 35 hospitals with units indicated that they would like to send a total of 188 nurses to a center for training. Assuming that at least one nurse would be sent from each of the 24 hospitals which did not answer this specific question, a minimum of 212 nurses from all 59 hospitals would be the estimated number who would be sent for training. Of those hospitals with definite plans for coronary care units, 56 indicated they

would like to send 280 nurses for specialized training. If, similarly, the 28 non-reporting hospitals in this category sent one nurse each, the minimum number of nurses to be sent for training would be 308 from all 84 hospitals.

Discussion

It is generally agreed that, in a properly run coronary care unit, nurses should be trained and authorized to perform cardiopulmonary resuscitation and defibrillation, to begin cardiac pacing and, within described limits, to give drugs in emergency. Responses to questions in the survey regarding these specific tasks indicated that coronary care unit nurses are either not fully utilized or that the level of training is inadequate for them to be permitted to perform these tasks.

Under-utilization of trained nurses is perhaps due to fear of medical-legal repercussions by either the nurses themselves or hospital administrators. This fear might be alleviated by reference to the joint statement by the California Heart Association, California Medical Association and California Nurses' Association* which recognizes the need for properly trained coronary care nurses to perform life-saving measures in the absence of and under the orders of a physician. This statement, while not a legal precedent, provides support of these professional associations and recognizes the expanded role of the coronary care unit nurse as "standard practice" under the circumstances.

The other reason for nurses not to perform the required life-saving tasks in a coronary care unit is, of course, lack of proper training. This survey indicated a definite desire by nursing directors and willingness on the part of hospital administrators, where there were coronary care units in existence or planned, to send at least some of their nurses for such training at specialized centers.

Extension of estimates made from the survey indicates that approximately 500 nurses would be sent to specialized centers if facilities were available. As this number far exceeds the space available at existing training centers, plans should be considered to increase the availability of center training either by expanding existing centers or establishing new ones.

The estimate of 500 nurses requiring center training is far below the actual number of coro-

* Acute cardiac care—The role of the registered nurse, Calif. Med., 104:228, Mar. 1966.

nary care unit nurses, all of whom should receive proper training. The consensus at the coronary care unit conference held in Washington in June 1967 was that coronary care unit head nurses, in-service educators and supervisors should receive intensive initial training of four weeks or longer at a specialized center.

Although it would be preferable to train all coronary care unit nurses by intensive four-week courses, this is not practical at present. Perhaps the best solution to training coronary care unit staff nurses is to establish local training facilities in one or more hospitals. The faculty for these training programs will be coronary care unit medical directors, cardiologists and internists, and well trained coronary care unit nurses from the local community, used in rotation. Training of this type would be less intensive and of shorter duration—approximately two weeks.

In order for short term local training to succeed, however, it must be combined with adequate continuing in-service education programs in hospitals to which the nurses return. Thus, coronary

care unit staff nurses will receive adequate initial training and continuing education to bring them to and maintain them at a high level of proficiency.

Another most vital area of coronary care unit activity at present is the need for properly trained physicians to direct coronary care units. Workers in the field are becoming increasingly concerned about over-emphasis given nurse training, to the almost total exclusion of physician training programs. In order for a coronary care unit to provide proper patient care, it must be directed by a qualified physician skilled in coronary care unit techniques. The coronary care unit director is the cornerstone of all coronary care unit activities. He must be trained in coronary care unit techniques, in proper administration of the unit and in methods of instruction necessary for in-service education for nurses and continuing education for physicians.

Staff physicians who admit and treat patients must also be cognizant of new techniques, new administrative policies and new nursing functions in coronary care units. This orientation could be accomplished by short-term symposia run by interested professional or voluntary agencies.



The Long-Acting Thyroid Stimulator

JOSEPH P. KRISS, M.D., *Stanford*

IN 1956 ADAMS and Purves, during the course of attempting to bioassay the thyrotropin (TSH) content of human sera, observed that the sera of some patients with hyperthyroidism contain a substance which stimulates the thyroid gland in a manner different from that of TSH.¹ This substance, originally thought to be an abnormal thyroid stimulating hormone,² was later termed "thyroid activator"³ and "abnormal thyroid stimulator."⁴ More recently the appellation long-acting thyroid stimulator (LATS) has been employed because it calls attention to the characteristic feature of the bioassay response which distinguishes the substance from TSH.

Following preparation of the test animal (mouse or guinea pig) successively by low-iodide diet, ¹³¹I-iodide injection, and suppression of endogenous TSH secretion by thyroxine administration, the response to the administered test substance is determined by measuring the amount of ¹³¹I radioactivity which appears in the blood upon release of labeled thyroid hormone and iodide from the thyroid gland. Whereas a maximal assay response is observed two or three hours after the intravenous injection of a given dose of TSH, the maximal response following injection of serum containing LATS occurs after eight or nine hours, or later.

Adams' and Purves' observation was soon confirmed by McKenzie⁵ and by Munro.⁶ Each group of investigators found that LATS could be detected in the sera of 30 percent or more of patients with Graves' disease, but rarely if at all in the sera of normal subjects. Adams and coworkers further showed that LATS was fully active in animals even after hypophysectomy.⁷ This observation indicated that LATS acted directly on the thyroid, and that

normal pituitary TSH played no part in the biologic response observed after LATS injection. Early thinking, however, remained oriented to the probability that LATS was an abnormal pituitary hormone related to TSH. However, support for the concept of the hypophyseal origin of LATS was not forthcoming from studies performed on thyrotoxic patients. Extracts of pituitary glands obtained from several such patients whose sera contained LATS yielded TSH but not LATS.⁸⁻¹¹ Furthermore, LATS was found in the serum of some thyrotoxic patients even after hypophysectomy.^{9,12} The accumulated evidence thus dispelled the notion that LATS was an aberrant form of TSH or that its site of synthesis was the pituitary gland. The thyroid gland, thymus, liver, spleen, pineal, hypothalamus, and the medulla of the brain were also excluded as sites of production of LATS.¹³ The probable site of synthesis of LATS was suspected only after the nature of LATS itself became more clearly known.

While LATS appeared to be a protein as judged by its precipitation by such agents as alcohol,¹⁴ early attempts to separate it from the other serum proteins by electrophoresis were not successful.¹⁵ With the availability of the method of gel filtration for separation of serum proteins, McKenzie provided evidence that LATS was found in that fraction of the serum proteins which was relatively enriched in 7S (γ G) globulins.¹⁶ Kriss, Pleshakov and Chien, using a highly potent serum obtained from a patient with pretibial myxedema, modified the McKenzie assay⁵ to adapt it for quantitative work.¹⁷ It was shown that LATS was fully active when given intraperitoneally and that responses were satisfactorily measured 24 hours after injection. The dose-response relationship over the full response range was described, and a working range of assay response was delineated which permitted reasonably accurate quantitative measurement of LATS concentration in serum and the vari-

From the Departments of Medicine and Radiology, Stanford University School of Medicine, Stanford.

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Reprint requests to: Division of Nuclear Medicine, Stanford University School of Medicine, Stanford 94305.

ous protein fractions derived from it. The method thus provided a means of assessing yield, recovery and purity.

By use of this method, the earlier observations of McKenzie and of Adams linking LATS to the serum globulins were extended and refined. Fractionation of the serum by acid salt precipitation followed by chromatography on DEAE-Sephadex yielded a fraction of high LATS content with a purification factor of about 8 to 10. This protein fraction was subjected to a variety of analytical procedures, including paper electrophoresis, double diffusion in agar gel, immunoelectrophoresis and ultracentrifugation, and was shown to contain only γ G globulin. Furthermore, it was shown that anti- γ G antibody, obtained from sheep that had been immunized against normal human γ G globulin, completely inactivated LATS present in serum or in purified LATS fractions.¹⁷ In independent studies, employing different methods of protein separation and analysis, Meek and coworkers¹⁸ also came to the conclusion that LATS was a γ G globulin. More recently, Miyai and Werner have confirmed these conclusions.¹⁹ In 1965 Dorrington and Munro presented data which suggested that LATS might be a B₁A globulin.²⁰ However, a more recent publication from that laboratory²¹ indicates that their earlier view has been abandoned, and they are in agreement with the conclusions reached in other laboratories. Thus the γ G nature of LATS seems to be securely established.

The knowledge that LATS was a γ G globulin led logically to the hypothesis that LATS was an antibody which, like other antibodies, was synthesized by lymphocytes.^{17,22} A large measure of support for this hypothesis has come from a number of biochemical, biological, immunological and clinical observations.

Biochemical Studies

Partial degradation of bivalent γ G antibody molecules may be accomplished by proteolytic digestion with pepsin, following which a fragment of reduced size may be recovered which retains the bivalent character of the parent molecule.²³ More extensive digestion of γ G globulin may be achieved by papain, an agent which degrades the molecule to even smaller fragments which are univalent with respect to antigen combining sites.²⁴ It was, therefore, of interest to study the effects of these two enzymes upon the biologic activity of

LATS sera or purified preparations. Early studies by McKenzie had indicated that the prolonged thyroid stimulating activity of LATS was preserved after papain digestion sufficiently extensive to yield fragments estimated to be much smaller than γ G globulin.²⁵ However, when Kriss and coworkers digested LATS with papain using a method known to cleave γ G antibody molecules into univalent antibody, about 95 percent of the long-acting thyroid stimulating activity was lost.¹⁷

A partial clarification of these apparently divergent results was provided when Meek and coworkers showed that the fragments of papain digestion retained thyroid stimulating properties, but they were now "short-acting" or "TSH-like" in nature.¹⁸

Question then arose as to whether LATS-globulin was a protein-pituitary TSH complex which in that form was "long-acting," but which on proteolytic digestion yielded the TSH moiety. Kriss and coworkers²⁶ as well as Dorrington and his associates²¹ answered this question in the negative by showing that the activity of the thyroactive fractions obtainable after papain or pepsin digestion could be completely abolished by anti-human γ G antibody but not by anti-human TSH antibody. Carrying the degradation of the LATS molecule even further, the Kriss group found that following reduction and alkylation of the fragment derived from papain digestion of LATS γ G, column chromatography of the mixture resulted in the isolation of a thyroactive fragment whose biological activity was not affected either by anti-human TSH or anti-human γ G antibodies.²⁷ The chain derivation of this fragment has not been established. However, subsequently, we found* that it can be inactivated by sheep anti-human Fab antibody (that is, antibody prepared by immunization of sheep with the univalent papain fragment of normal γ G globulin).

The observations summarized above indicate that, even after partial degradation of the native LATS molecule by papain, the thyroid stimulating properties of the resultant fragment reside in a moiety which is part of the γ G molecule and which is not TSH. The γ G antibody molecule may also be partially degraded in a different manner by reduction of the disulfide bonds and subsequent alkylation, procedures which permit the later individual separation of the constituent A and B chains which are linked together in the parent molecule.^{28,29} When LATS globulin was so treated,

*Unpublished observations.

it was found that the biologic activity of the product was generally greatly reduced. Such activity as was retained resided chiefly in the A chain.^{18,30} Recombination of the separated A and B chains of a LATS preparation restored some of its lost biologic activity.³¹ If LATS were a γ G antibody, the univalent thyroactive LATS papain fragment would consist of the B chain and that portion of the A chain (Fd fragment) which participates in the antibody combining site. The fact that the papain fragment is precipitated by anti-human B chain antibody²⁶ is thus also consistent with an antibody nature of LATS γ G.

Recently Volpe and coworkers suggested the possibility that LATS is not an antibody, but arises without previous antigenic stimulation as the product of a cell line derived by clonal selection.^{26a} The mechanism of clonal selection has also been invoked by McKenzie, who has postulated that a person with Graves' disease may have an inherited predisposition to produce a "forbidden clone" of immunologically competent cells—that is, a mutation of lymphocytes, which could synthesize LATS.^{26b}

We have obtained evidence which we believe is inconsistent with the clonal selection hypothesis. The γ G globulin of normal persons can be divided into two groups according to their reactivity with appropriate antisera.^{26c} The antigenic determinants responsible for this particular aspect of the heterogeneity of γ globulins are located on the B chains. In normal human sera approximately 60 percent of γ globulin molecules carry the antigenic determinants of Group 1, while about 30 percent bear determinants of Group 2.^{26c} Individual mature lymphoid cells in spleen and lymph node, however, produce only γ G globulin of one type—either Group 1 or Group 2. The clonal selection hypothesis, therefore, would predict the formation of a γ G product which is either of Group 1 (kappa) or Group 2 (lambda) type, but not both.

Thus, if LATS were the product of a cell line derived by clonal selection, in any given patient the LATS γ G globulin should be of one antigenic type only. In recent studies we showed that the serum LATS activity of seven different patients invariably could be inactivated partly by anti-k and partly by anti- λ antiserum.^{26d} Such inactivation is interpreted to mean that each patient possesses two types of LATS γ G globulin molecules, those with kappa (κ) type B chains and others with lambda (λ) type B chains.

LATS, therefore, is not the product of a cell line derived by a monoclonal selection process, a finding which would appear to be incompatible both with the "non-antibody" hypothesis of Volpe^{26a} and of McKenzie's postulate of an inherited predisposition to produce a "forbidden clone" of immunologically competent cells capable of synthesizing LATS.^{26b} The inactivation of LATS by anti-k and anti- λ antibodies, antibodies directed solely to determinants on the B chain, may be considered additional proof of the immuno-globulin nature of LATS.

Biological Studies

The possible antibody role of LATS has logically led investigators to determine whether LATS, like other antibodies, is synthesized by lymphatic tissue. The author tried unsuccessfully to extract LATS from excised lymph nodes taken either from the pretracheal or inguinal region in a man with a high serum LATS concentration. However, McKenzie and Gordon showed that LATS, albeit in small amounts, could be recovered from the culture medium of phytohemagglutinin-stimulated lymphocytes obtained from the blood of a patient seropositive for LATS.^{13,26b} These findings have been confirmed by Miyai and coworkers.^{26c} The capability of such lymphocytes to synthesize antibody *in vitro* was shown by demonstrating their ability to incorporate C¹⁴-labeled amino acids into both A and B chains of γ G globulin.³²

Immunological Studies

Proof that LATS is an antibody depends ultimately on the demonstration that a specific immunologic reaction takes place between LATS and an identifiable antigen. Furthermore, it would seem essential that such a demonstration also explains the fact that LATS derived from humans with thyroid disease is biologically active not only in the human, (see later discussion of neonatal thyrotoxicosis) but in the mouse and guinea pig, while being apparently inactive in the chick.³³

Evidence that LATS interacts with another tissue and is thereby removed or inactivated was first provided by Kriss and coworkers when they demonstrated apparent LATS removal from sera incubated with dog or human thyroid tissue slices or homogenates.¹⁷ This removal, while species non-specific, was apparently organ-specific since negligible LATS was removed upon incubation of the sera with a variety of other tissues including

brain, liver, kidney, spleen, adrenal and testis. Pinchera and coworkers, on the other hand, failed to observe LATS removal on incubating sera with thyroid slices and cell "membranes" obtained at operation from a patient who was seropositive for LATS.³⁴

A number of other groups of investigators have, however, confirmed and extended the findings reported by Kriss and coworkers. Beall and Solomon fractionated human thyroid cells by centrifugation and demonstrated that several components, especially the insoluble microsomal fraction (containing also cell membranes) were capable of removing or inactivating LATS *in vitro*.³⁵ Thyroid glands obtained at autopsy are as suitable as those obtained fresher at operation. Fractions from other human tissues prepared similarly were inactive with respect to LATS removal. Further work in that laboratory has tended to confirm although not completely establish the immunologic nature of the interaction between LATS and the thyroid tissue component.³⁶

Of considerable interest and probable importance is the fact that LATS may be released from the thyroid cell component by treatment with buffer at pH 3.5, with apparent increase in purity of the LATS thus recovered. Unfortunately, the LATS was recovered in low yield, about 15 to 20 percent.

Findings similar to those of Beall and Solomon have been reported by several other groups. Dorrington and coworkers have confirmed the removal of LATS upon incubation of active sera with the microsomal fraction of human thyroid and found on further processing of this fraction that most of the LATS-combining activity was recovered in the endoplasmic reticulum.³⁷ El Kabir and coworkers found, in addition to the removal of LATS by thyroid, some non-specific removal of LATS by other tissues—kidney, for example.³⁸ A considerable variability was found amongst different thyroid preparations with respect to LATS removal or inactivation.

The initial experience of these investigators would suggest that thyroid tissue obtained from thyrotoxic and LATS-positive individuals interacts less effectively with LATS than does thyroid tissue obtained from other sources. However, this experience is not uniform, and it is not clear that the histologic and functional state of the gland is the determining factor in interacting with LATS. In fact, a recent report by Adams and Kennedy,³⁹

while incidentally confirming the interaction of LATS with thyroid tissue, describes the finding in certain thyrotoxic sera of yet another γ G globulin which does not possess thyroid stimulating properties, but which is capable of interfering with the interaction between LATS and its thyroid tissue binding site. These investigators have tentatively called this γ G globulin, presumably also an antibody, the LATS protector, and postulate that it shares partial antigenic specificity with LATS. Presumably such a substance, by interfering with the binding of LATS to its specific binding site, might, if present in sufficient quantity, also greatly reduce the biologic effectiveness of LATS *in vivo*. The clinical and biological significance of this most recently reported factor remains to be determined.

Dissent from the antibody hypothesis has been voiced by Burke,⁴⁰ who calls attention to the fact that many of the standard immunologic methods employed to demonstrate antigen-antibody interaction have not succeeded in demonstrating such interaction with LATS and its presumed thyroidal antigen. Also cited is the inability to show LATS activity in the sera of guinea pigs immunized with various human thyroid fractions. However, preliminary reports from other workers indicate that injections of "thyroid antigen" have now proved successful in eliciting the production of LATS by the immunized animal. Thus, Pinchera and coworkers claim to have induced the production of LATS in rabbits by immunization with thyroid cell particulate fractions,⁴¹ and similar results also have been reported by Solomon and Beall.⁴² The latter workers report that their immunized LATS-producing animals showed evidence of thyroid damage and no clinical stigmata of thyrotoxicosis. Thus, it is possible that the rabbit LATS was elaborated not in response to the injected human antigen, but in response to a rabbit thyroid antigen released as a result of thyroid injury which the human antigen may have caused.

While these findings raise a doubt as to whether the induced rabbit LATS is directed against a human or a rabbit thyroid antigen, they nonetheless lend support to the concept that LATS is an antibody. A more detailed report is now available from these workers.^{26f} The thyroid stimulating activity in the serum of thyroid-immunized rabbits was intermediate in time course between thyrotropin and human LATS. The sera showed elevated protein bound iodine and thyroxine, balanced by markedly reduced resin uptake of ¹³¹I-triiodothy-

ronine. Thyroidal ^{131}I uptake and serum PB ^{131}I and conversion ratio were unaffected by immunization. The sera also contained precipitating and hemagglutinating antibodies against human thyroglobulin and antibodies which fixed to both colloid and cytoplasm of thyroid tissue sections.

McKenzie recently summarized his findings in similarly performed experiments.^{26b} He concluded that the rabbit thyroid stimulator is more readily induced by immunizing animals against whole-thyroid extract than against microsomes. Neither group of investigators has as yet presented unequivocal evidence that the rabbit stimulator is inhibited by anti-rabbit γG antibody, so that the nature of the thyroid-stimulating activity in the serum of thyroid-immunized rabbits has not been conclusively established. Beall and Solomon^{26f} alluded to a coming publication which will present evidence that the sera contain both TSH and a thyroid stimulating γG globulin. It would also seem of importance to repeat the studies, using animals with the thyroid gland removed, in order to better evaluate the role of the animal's own thyroid gland in the induction of the stimulator.

The earlier inability to demonstrate an immunologic reaction between LATS and thyroid tissue by fluorescence microscopy¹⁷ may also have been overcome. A preliminary report by Blum and coworkers described a cross reaction between fluorescein-labeled guinea pig anti-rabbit globulin and a human globulin, believed to be LATS, which binds to the cytoplasm of the thyroid cell.⁴³ Thus, it is this reviewer's judgment that, while proof that LATS is an antibody still awaits definitive demonstration, the bulk of evidence supports the antibody hypothesis.

Comparative Studies of LATS and TSH

One should not conclude this portion of the discussion without mention of studies comparing the actions of LATS and TSH or studies designed to determine if a competitive relationship exists between the two substances. The thyroid stimulating properties of both LATS and TSH were found to be decidedly inhibited by pre-treatment of the test animal for 24 hours with both actinomycin D and puromycin.¹⁷ These findings were interpreted as indicating a possibility that the site of action of the two stimulators was the same and may be at the level of translation of the genic information of the thyroid cell. Subsequently, McKenzie reported that whereas incorporation of C^{14} amino acids into

thyroid protein *in vivo* was inhibited by either puromycin or actinomycin D given a half hour to an hour earlier, these antibiotics inhibited radioiodine release from the gland only when they were given 8 to 15 hours previously.⁴⁴ He concluded that fresh protein or RNA synthesis does not appear to be necessary for the acute effects of either TSH or LATS to be manifested. No clear qualitative differences in the effects of the two stimulators or in their inhibition by antibiotics were seen. This finding, together with the observation that the administration of LATS appeared to prevent completely the response to a subsequent TSH injection, also led to the suggestion that the two stimulators act at the same site in the thyroid gland. A similar reasoning might apply to the finding of Burke that pre-incubation of thyroid microsomes with TSH significantly reduces their ability to inhibit or remove LATS.⁴⁵ In studying the effects of TSH and LATS on the intracellular appearance of colloid droplets and release into the blood of ^{131}I , Shishiba and coworkers concluded that the effects were qualitatively similar but that LATS had a longer latency.⁴⁶ The chick thyroid is responsive to bovine TSH but apparently non-responsive to LATS.³³ It is not clear whether this difference in response is qualitative or quantitative (compared with the mouse the chick is relatively insensitive to TSH).

The effects of LATS and TSH have also been compared in *in vitro* systems. By study of sheep thyroid slices, Scott, Good and Ferguson found that LATS and TSH have similar actions in increasing glucose oxidation and lactate formation.⁴⁷ However, quantitative differences were observed with respect to their effect on phospholipogenesis, LATS being relatively more effective in stimulating the incorporation of p^{32} orthophosphate into lecithin and the formation of neutral lipid from glucose. Field and coworkers compared the effects of TSH and LATS on carbohydrate and phospholipid metabolism *in vitro* and found that whereas qualitatively their effects are similar, the action of LATS is observable only after a latent period lasting several hours.⁴⁸ McKenzie reported that nicotinamide inhibits the responses of a subsequent injection of both TSH and LATS.^{26b} He also showed that theophylline *in vivo* potentiates the assay response of injected TSH and LATS, and postulated that cyclic AMP may be involved in the mediation of the response to both stimulators.^{26b} He offered the intriguing suggestion that the phosphodies-

terase which hydrolyzes cyclic AMP may be the inhibitor (antigen) specific for the long acting thyroid stimulator. We have tested (unpublished observations) the possible LATS neutralizing effect of two phosphodiesterases: Neither beef heart nor rabbit brain phosphodiesterase, when incubated with LATS before injection of the mixture, caused any reduction in LATS activity. The effect of phosphodiesterase obtained from thyroid tissue remains to be determined.

In comparing the actions of TSH and LATS, despite their chemical dissimilarity, one is impressed with the fact that their biological actions so far studied are qualitatively similar. In some instances, both *in vivo* and *in vitro*, the effect of LATS appears to be associated mainly with a delay in the onset of action. Because of these findings, one might predict that elucidation of the biochemical mechanism of action of either one of the stimulators will contribute materially to our understanding of the action of the other.

Significance of LATS

Hyperthyroidism in adults

Ever since Adams' and Purves' original observation of the assay phenomenon characterizing LATS,¹ there has been a tenable thesis that LATS is the causal agent of Graves' disease. The finding that LATS was frequently detected in the sera of thyrotoxic subjects and not in the sera of normal persons¹⁵ was the major factor contributing early to this view. Other factors were (a) indications that the pituitary-thyroid axis was normal in hyperthyroidism,⁴⁹⁻⁵² (b) failure to demonstrate elevated levels of TSH in hyperthyroidism,⁵³⁻⁵⁶ and (c) the occurrence of hyperthyroidism in hypophysectomized individuals.⁵⁶⁻⁶⁰

Certain facts, however, suggested the need for caution in accepting a causative role for LATS. First, LATS is not uniformly detected in the sera of patients with thyrotoxicosis. Frequencies of detection varying from about 25 to 80 percent have been reported. When allowance is made for non-specific responses, LATS is detectable in about 30 percent of untreated hyperthyroid patients on assay of unfractionated serum.^{10,34,61-63} All investigators agree that florid hyperthyroidism may be present in a person who is seronegative for LATS, and that the clinical severity of thyrotoxicosis bears no obvious relationship to the LATS assay response of the patient's serum. However, Major and Munro reported a correlation between LATS

titer and radioiodine turnover.¹⁰ A more recent statistical analysis from Munro's laboratory reiterating their earlier claim employs the dubious maneuver of excluding LATS-negative but thyrotoxic subjects from consideration in the analysis correlating the two parameters.⁶⁴ Noguchi and coworkers found a rough correlation in patients treated by thyroidectomy between thyroid cell height and LATS assay response.⁶⁵ It has been claimed that observations such as these support a causal role of LATS in the pathogenesis of hyperthyroidism.

A second reason for skepticism to a causative role for LATS is that cure of thyrotoxicosis is frequently not accompanied by disappearance of LATS from the blood. In fact, LATS may persist in the circulation even after hypothyroidism supervenes, in which event both LATS and TSH may be detected in the serum.^{49,62,66} A third reason is that LATS may be found in persons with thyroid disease or with ophthalmopathy who have never had thyrotoxicosis.^{10,14,15,67} In some persons circulating LATS was first detected only after radioiodine treatment for hyperthyroidism,^{26,62} a finding which led us to question the initiating role of LATS in the pathogenesis of hyperthyroidism. Finally, LATS has not been found in the sera of patients with that form of thyrotoxicosis associated with single or multiple hyperfunctioning adenomata.^{34,68}

Lack of sensitivity of the LATS bioassay may account for many, perhaps all, of the instances in which LATS could not be detected in the sera of patients with active thyrotoxicosis. Support for this view comes from evidence that serum protein concentration or purification procedures may succeed in yielding LATS-positive fractions derived from LATS-negative sera of thyrotoxic patients.^{63,69} As another explanation for the failure to detect LATS in thyrotoxic subjects, it has also been suggested that LATS may act primarily as a transient trigger for some long-lived thyroid disturbance.¹² From the evidence available at present it would seem reasonable to accept relative insensitivity of the LATS assay as the main reason why hyperthyroid patients may be sero-negative for LATS.

We have postulated that in order for LATS to initiate thyrotoxicosis, the patient must have a normal or nearly normal thyroid gland.⁶² A diseased thyroid gland, despite the presence of LATS, may be incapable of responding to a degree which renders the subject thyrotoxic; on the contrary, he may remain euthyroid or hypothyroid.^{70,71} Thus,

two factors may be essential for the maintenance of the thyrotoxic state: (a) circulating LATS and (b) a thyroid gland capable of responding to a thyroid stimulator by increasing its thyroxine synthesis and secretion to abnormally high levels. Two challenging questions immediately arise: (1) whence comes LATS?, and (2) what is the pathogenesis of the thyroid disorder which renders some glands apparently unresponsive to thyroid stimulators, either LATS or TSH? It is this reviewer's opinion that these are related questions which may share in a common answer. The discussion of these questions will be deferred to later sections of this review. Meanwhile, it is appropriate to discuss neonatal thyrotoxicosis, a unique and highly interesting form of thyrotoxicosis in which there appears to be little doubt about the origin of the LATS.

Neonatal thyrotoxicosis

Neonatal thyrotoxicosis is a rare form of thyrotoxicosis which is characterized by several features that distinguish it from hyperthyroidism occurring later in childhood, adolescence or adulthood. Clinical evidence of hyperthyroidism exists at birth or there is an abrupt onset of the disorder within several days of age. Invariably, the mother has or has had thyrotoxicosis, usually associated with exophthalmos. The illness in the infant, if not leading to immediate fatality, is short-lived and is followed by permanent remission, with or without therapy.

Major and Munro were the first to report findings which suggested that LATS was implicated in this form of thyrotoxicosis.⁷² They had observed a woman who twice had given birth to infants who died within a few days with severe hyperthyroidism. Examination of the mother's serum revealed an extraordinarily high titer of LATS. Subsequent studies by Rosenberg and coworkers,⁷³ McKenzie,⁷⁴ Sunshine and coworkers,⁷⁵ and Holmes and his associates⁷⁶ demonstrated LATS not only in the sera of women who had given birth to thyrotoxic infants, but also in the sera of afflicted infants themselves.

Of considerable importance was the fact that the blood level of LATS in such infants was found to decline rapidly with age.^{74,75} McKenzie estimated that LATS disappeared from the neonatal blood with a half-time of the order of one or two weeks.⁷⁴ In the case studied by Sunshine and coworkers LATS was measured serially in both maternal and infant sera for the first few weeks after

delivery.⁷⁵ LATS was detected in both sera when the infant was eight days of age. Thereafter, the serum LATS concentration of the infant fell progressively with a calculated half-time of six days, while that of the mother remained constant for several months. LATS was no longer detected in the infant's serum at the age of 25 days, and at that time all antithyroid therapy was discontinued. The remission, which probably had been initially induced by drug therapy, was maintained despite its withdrawal.

The data summarized above constitute strong evidence that neonatal thyrotoxicosis is, like erythroblastosis fetalis, a disease of transplacental passage of noxious γ G globulin—LATS in the former case and anti-Rh+ antibody in the latter. The fetal level of γ G globulin is low until the fourth or fifth month of gestation and does not reach the maternal level until the eighth or ninth month.⁷⁷ Therefore, it is likely that γ G globulin is passed to the fetus relatively late in pregnancy. Hence, the infant is not likely to have hyperthyroidism for an appreciable time *in utero*, or to have goiter or other clinical signs of disease until after a few days of life.^{73,75,78-81} It has been suggested that, in order to predict likely candidates for neonatal thyrotoxicosis, LATS assays should be performed late in gestation in all pregnant women with thyrotoxicosis or a history of that disorder.⁷⁵

The finding of a very high LATS titer has led to consideration of attempting to lower maternal serum LATS concentration by corticosteroid treatment^{17,82} before delivery, or of exchange transfusion of the neonate.⁷⁵ It will be of interest to see whether future experience will show that low maternal serum LATS concentrations are associated with correspondingly low concentrations in the infants' serum and short-lived or mild hyperthyroidism.

In the case described by Sunshine and coworkers,⁷⁵ the fetal serum LATS concentration was considerably higher than the maternal, a finding which is consistent with recent observations indicating that the permeability of the placenta by γ G globulin in the direction of mother to fetus is greater than that in the opposite direction.⁸³ Exophthalmos or periorbital edema have also been reported in infants with neonatal thyrotoxicosis.^{73,75,76,84} In such cases, the ophthalmic signs disappeared as the thyrotoxicosis waned, or shortly thereafter. These observations suggest that, in addition to being the agent responsible for neo-

natal thyrotoxicosis, LATS may be causally related to the more serious ophthalmic manifestations of Graves' disease. The possible relationship between LATS and ophthalmopathy will be considered in the following section.

Ophthalmopathy

Mention has already been made of the fact that little, if any, correlation has been found between the clinical severity of thyrotoxicosis and the patient's serum LATS titer. In several series there appeared to be a somewhat better correlation between serum LATS and the presence of exophthalmos,^{11,15,34,62,65,85,88} However, the correlation was not always impressive, and not infrequently severe infiltrative ophthalmopathy has been seen in patients with LATS-negative sera.

Recent work in the author's laboratory has revealed new evidence relevant to the pathogenesis of ophthalmopathy⁶² defined as those ophthalmic manifestations of Graves' disease which singly or in combination present as proptosis, periorbital or conjunctival edema, excessive lacrimation, ophthalmoplegia or failing vision. Exophthalmometry and determinations of serum levels of LATS, TSH and anti-thyroglobulin (anti-TG) were performed in previously untreated hyperthyroid patients before and after radioiodine treatment. The presence of ophthalmopathy before treatment was positively correlated with the detection of LATS, but not of anti-TG, in the serum. Most patients whose serum was initially LATS-negative remained sero-negative after treatment, and no ophthalmic complications developed in them.

In three patients LATS was first detected in the serum several months after treatment at a time when the subjects were clinically euthyroid. In each case the appearance of LATS in the circulation shortly preceded or coincided with the onset of an ophthalmopathy, which was severe in two of the subjects. Antibodies to thyroglobulin or to thyroid cell components were detected in the *pre-treatment* sera of each of the patients in whom ophthalmopathy later developed. Rises in anti-TG titer also occurred after therapy, but not until after the appearance and rise in concentration of LATS, and they did not correlate with the onset of clinical signs and symptoms of ophthalmopathy. TSH was invariably not detectable in pre-treatment sera, nor was it detected at any time in the sera of the two patients in whom severe ophthalmopathy developed.

From these results we concluded that LATS

bears a close, perhaps a causal though indirect relationship to ophthalmopathy. We have also concluded that neither TSH nor anti-TG antibody is directly implicated in the onset of ophthalmopathy. Presence of anti-TG antibody relatively frequently in the sera of untreated thyrotoxic patients may be taken to indicate that a state of thyroid autoimmunity existed in such patients before radioiodide treatment. Such autoimmunity may result from (a) stimulation of a normal immune mechanism by release of a cell constituent (antigen) not normally found extracellularly, or (b) malfunction of the immune mechanism.

Irvine espoused the view that thyroid autoimmunity may be a result of malfunction of the immune mechanism,⁸⁹ a view that perhaps better explains the frequent coexistence of thyroid and gastric antibodies in the serum of thyrotoxic patients⁹⁰ or the occasional association of hyperthyroidism with myasthenia gravis,^{91,92} a disorder which may be reproduced experimentally in rats and guinea pigs by autoimmunization with thymus extracts.⁹³ We favor the former view—that is, that previous thyroid injury was the most likely cause of the development of the autoimmune state—and we postulate that such injury resulted also in release of LATS antigen and subsequent synthesis of LATS by lymphocytes.

This, then, is our answer to the question posed in a previous section: Whence comes LATS? In this context, we regard thyroidal ¹³¹I as an agent of physical injury, which may cause a *renewed* release of LATS-antigen (as well as other antigens), and lead to an anamnestic LATS antibody response. Ophthalmopathy and pretibial myxedema (see following section) seem to develop as LATS, presumably at a time of antibody excess, appears in maximal concentration in the serum.

Whether LATS does or does not play a causal role in ophthalmopathy is a matter of speculation. If it does, it probably acts indirectly, since not all the signs of ophthalmopathy receded when the serum LATS concentration fell. We have suggested that the tissue abnormalities characteristic of ophthalmopathy may be the result of the toxic effects of locally deposited antigen-antibody complexes or may be due to a delayed hypersensitivity reaction involving sensitized lymphocytes.⁶² McKenzie's recent data obtained from patients with pre-existing (rather than developing) ophthalmopathy did not lead him to associate ophthalmopathy with LATS nor the appearance of the latter with ¹³¹I-

iodide therapy.⁹⁴ However, a recent report by Wyse and coworkers corroborates the association of ophthalmopathy, LATS seropositivity and evidence of thyroid injury (Hashimoto's thyroiditis).⁹⁵ We have observed LATS in the serum of two patients whose thyroid region was irradiated during treatment for Hodgkin's disease. It may be relevant that hyperthyroidism has also been observed to develop soon after subacute thyroiditis of the de Quervain type.⁹⁶

Catz and his associates have advocated total ablation of the thyroid for treatment of the ophthalmopathy of Graves' disease, pointing out that the resultant improvement in their patients so treated was accompanied by a fall in serum LATS to undetectable levels.^{97,98} The efficacy of such treatment has recently been challenged by Werner and coworkers.⁹⁹

Pretibial myxedema

The author and his coworkers have emphasized that patients with pretibial myxedema are especially frequently seropositive for LATS.¹⁷ A similar association has been observed by Pimstone and coworkers,⁸⁷ Solomon et al,⁸⁸ Pinchera et al,³⁴ Webster et al,¹⁰⁰ and Carneiro et al.⁶³ Our current cumulative experience indicates that LATS was detected in 19 of 21 consecutive patients with pretibial myxedema.¹⁰¹ In many of these patients, serum LATS concentration was very high, much higher than is customarily observed in uncomplicated thyrotoxicosis.

It is our impression, as yet not statistically validated, that serum LATS concentration is relatively the highest in those few patients with pretibial myxedema and ophthalmopathy who present with the additional complication of thyroid acropachy.^{102,103} Thus, there appears to be at least a rough correlation between the serum LATS level and certain clinical states, namely, zero in normal persons, low or barely detectable levels in uncomplicated hyperthyroidism, moderate levels in ophthalmopathy, high levels in pretibial myxedema, and perhaps highest levels in patients with thyroid acropachy.

In one of our documented cases⁶² the appearance of LATS in the circulation in high concentration preceded by several weeks the sudden onset of pretibial myxedema. We have observed a similar sequence of events in three additional recently observed patients. It seems reasonable to conclude that LATS has some special significance with re-

spect to the onset and maintenance of the lesions of pretibial myxedema. However, it is as yet as speculative to assign a causal role for LATS in that disorder as it is in ophthalmopathy. In view of the demonstrated close clinical correlation between pretibial myxedema and ophthalmopathy,^{17,101,104,105} one should not be surprised if it should later be demonstrated that LATS plays essentially similar roles in the pathogenesis of each of these complications of Graves' disease.

Down's syndrome (mongolism)

A recent report described the finding of LATS in the sera of some euthyroid but goitrous patients with mongolism.⁶⁷ Children with Down's syndrome and their mothers have a significantly higher frequency of thyroid autoantibodies than controls.^{106,107} Clinical thyroid abnormalities were detected in 20 percent of the mothers of Down's syndrome patients.¹⁰⁶ These findings have raised question as to whether the thyroid antibodies are the cause or the effect of the child's aneuploidy.

Fialkow favors the view that maternal thyroid antibodies directly or indirectly predispose to the chromosomal abnormality characteristic of Down's syndrome.¹⁰⁶ Without taking a stand on the question at issue, we may point out that the finding that LATS may be detected in the sera of some patients with mongolism is consistent with the hypothesis expressed in earlier paragraphs, namely that the occurrence of thyroid injury, whether genetically, physically, chemically or virally induced, may lead to the formation of various thyroid autoantibodies, including LATS. While Mosier's patients with LATS remained euthyroid although goitrous, perhaps due to limited thyroid response capacity,⁷¹ thyrotoxicosis might be expected to occur occasionally in similar patients if LATS were produced and thyroid injury were not permanent or unduly severe. Hyperthyroidism has, in fact, been reported in some patients with mongolism.^{108,109}

Some related comments and speculation on the therapy for Graves' disease and its complications

The role that ¹³¹I-iodide therapy and LATS appear to play with respect to the later development of ophthalmopathy has already been commented upon. Comparable studies are needed of thyrotoxic patients undergoing surgical treatment. It would not be surprising if the occasional occurrence of post-surgical progressive exophthalmos is also

found to be associated with changes in serum LATS concentration, possibly indirectly triggered by the thyroid damage unavoidable in performing operations on the thyroid gland. This author is not convinced that ^{131}I -iodide therapy offers any advantage over surgical operation with respect to the frequency with which ophthalmopathy develops after treatment.

In some cases the serum LATS concentration may fall as euthyroidism is induced by antithyroid drugs.¹¹⁰ In others, LATS titers may fall spontaneously. The author is inclined to believe that the disappearance of LATS from the plasma in some patients, particularly those with low LATS titer, probably represents a specific example of the general phenomenon of gradual decline of antibody titer with time following the original antigenic stimulus. Indeed, the spontaneous fall in serum LATS concentration may ultimately be found to account for those permanent remissions which occur after prolonged propylthiouracil therapy, while conversely, clinical relapses after such therapy may be associated with persistence of LATS in the serum. Such studies await the development of a much more sensitive method for measuring LATS in serum.

During corticosteroid therapy, especially if long continued, the serum LATS concentration may fall. Such an effect has been shown after oral as well as after local therapy in cases of pretibial myxedema.^{17,101} Snyder et al also reported a similar effect of corticosteroid therapy in patients with ophthalmopathy.¹¹¹ In view of the postulated antibody nature of LATS, it is of interest to note that prolonged corticosteroid therapy also causes decreases in serum anti-thyroglobulin antibody titers.¹¹² If LATS were the cause of hyperthyroidism, and if corticosteroid treatment is accompanied by reductions in serum LATS concentration, then one would anticipate that corticosteroid therapy might be effective in controlling the symptoms of thyrotoxicosis. Werner and Platman did in fact show that oral corticosteroids, administered as the sole treatment, induced remissions in three of five patients with hyperthyroidism.¹¹³ However, only one of these patients was seropositive for LATS before treatment, and one cannot be certain that the remissions were due to reductions in serum LATS concentration.

Apparently, prolonged corticosteroid therapy is required to elicit remissions in Graves' disease. However, even with short periods of treatment, a

suppressive effect of adrenocorticosteroids on thyroid function in hyperthyroid subjects has been observed.^{114,115} We have recently observed a patient with hyperthyroidism in whom local therapy of the legs (for associated pretibial myxedema) with fluocinolone acetonide cream induced a remission in thyrotoxicosis concomitant with a fall in serum LATS concentration.¹⁰¹ The systemic effects of the topically administered hormone were ascribed to transcutaneous absorption of the steroid. These observations suggest that systemic corticosteroid therapy, through its suppressive effect on serum LATS levels, may induce remissions in thyrotoxicosis.

Graves' disease appears to be initiated occasionally following the ingestion of desiccated thyroid,¹¹⁶⁻¹¹⁹ and in some reports of such cases the predominance of ophthalmic manifestations has been emphasized.^{117,118} This author has personal knowledge of at least four instances of apparent precipitation of ophthalmopathy occurring abruptly after the starting of relatively large doses of desiccated thyroid or after sudden and pronounced increase in the intake of this preparation.

Is it conceivable that bovine thyroid contains a substance identical to or related to the postulated LATS antigen which, when given in large amounts, may, in some patients, be absorbed from the gastrointestinal tract and initiate either a primary or a secondary immune response with resultant LATS production and the biologic sequelae thereof? Certainly the gastrointestinal tract may be permeable to antigenic proteins.¹²⁰⁻¹²³ The fact that human LATS γG exerts a biologic effect on the thyroid gland of other animals, such as mice and guinea pigs, indicates that the thyroid receptor ("antigen") is not species-specific. Hence it is not completely preposterous to imagine that a protein constituent of the bovine thyroid preparation in some instances may be capable of inducing the production of LATS.

In at least some of the patients, the hormonal therapy was given because of signs or symptoms of hypothyroidism or thyroiditis or both—that is, indications of previous thyroid injury. In those instances one could postulate the occurrence of an anamnestic immune response after challenge with desiccated thyroid. It is of some importance to establish in any future cases of thyroid hormone-induced Graves' disease whether desiccated thyroid or synthetic hormone was used as the therapeutic agent. For example, the occurrence of Graves' disease following ingestion of synthetic

thyroxine would be difficult to explain on an immunologic basis. A recent review of thyroid-hormone induced Graves' disease did indeed include mention of several cases in which purified hormone was administered.^{123a}

Finally, an additional and controversial area seems worthy of brief speculative comment. In the light of the previous discussion which emphasizes the immunologic basis for the development of Graves' disease, one might ask what possible role, if any, could severe emotional or neurologic disturbance play in the pathogenesis of Graves' disease. Many thyroidologists, including the present author, have been impressed repeatedly with accounts of individual patients which appear to point to unusual psychic stress or head trauma as states or events which trigger the onset of thyrotoxicosis. In the reviewer's experience, the severe psychic stress frequently occurred in the context of a situation of several weeks' or a few months' duration which the patient (but not necessarily the physician) views as catastrophic and for which the patient sees no solution, a state which may be designated descriptively as "catastrophic entrapment." One might reason that in such a situation, excitation of the central nervous system is reflected ultimately via hypothalamic neuro-endocrine pathways in excessive TSH secretion.

There is disagreement as to whether thyroid hormone secretion may be augmented under situations of psychic stress.^{124,125,126} Still to be obtained are the more crucial data on the effect of psychic trauma on circulating TSH levels, as measured by techniques sensitive enough to detect it in normal sera. In any case, in active hyperthyroidism, serum TSH is uniformly low or normal.^{127,128} A number of independent observations lead to the conclusion that in hyperthyroidism this suppression of pituitary TSH secretion reflects the existence of a normal endocrine feed-back inhibitor mechanism.^{49,50,62,127} Thus, the available evidence weighs heavily against a role for TSH in *maintaining* the thyrotoxic state. However, one cannot at present exclude the possibility that TSH is implicated *early* in the pathogenetic process leading to that state, that is to say, in the postulated original injury to the thyroid gland which leads ultimately to the immunogenic synthesis of LATS and, via this agent, to hyperthyroidism. Knowledge bearing on such a possibility will not be obtained easily.

REFERENCES

1. Adams, D. D., and Purves, H. D.: Proc. Univ. Otago. Med. School, 34:11, 1956.
2. Adams, D. D.: J. Clin. Endocr., 18:699, 1958.
3. McKenzie, J. M.: Trans. Assoc. Am. Physicians, 72:122, 1959.
4. Adams, D. D.: Endocrinology, 66:658, 1960.
5. McKenzie, J. M.: Endocrinology, 62:865, 1958.
6. Munro, D. S.: J. Endocr., 19:64, 1959.
7. Adams, D. D., Purves, H. D., and Sirett, N. E.: Endocrinology, 68:154, 1961.
8. Munro, D. S., Kilpatrick, R., Major, P., and Wilson, G. M.: First International Congress of Endocrinology, Copenhagen, 1969, Abst. 599.
9. McKenzie, J.: Proc. Roy. Soc. Med., 55:539, 1962.
10. Major, P. W., and Munro, D. S.: Clin. Sci. 23:463, 1962.
11. Purves, H. D., and Adams, D. D.: Fourth International Goitre Conference, London, 1960, Excerpta Med (XXVI), Abst. 36.
12. Becker, D. V., and Furth, E. D.: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome, 1965, Editors C. Cassano and M. Andreoli, Academic Press, N. Y., 1965, p. 596.
13. McKenzie, J. M., and Gordon, J.: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome, 1965, Editors C. Cassano and M. Andreoli, Academic Press, N. Y., 1965, p. 445.
14. Adams, D. D., and Kennedy, T. H.: Proc. Univ. Otago. Med. School, 40:6, 1962.
15. McKenzie, J. M.: J. Clin. Endocr., 21:635, 1961.
16. McKenzie, J. M.: J. Biol. Chem., 237:PC3571, 1962.
17. Kriss, J. P., Pleshakov, V., and Chien, J. R.: J. Clin. Endocr., 24:1005, 1964.
18. Meek, J. C., Jones, A. E., Lewis, U. J., and Vanderlaan, W. P.: Proc. Natl. Acad. Sci., 52:342, 1964.
19. Miyai, K., and Werner, S. C.: J. Clin. Endocr., 26:504, 1966.
20. Dorrington, K. J., and Munro, D. S.: Clin. Sci., 28:165, 1965.
21. Dorrington, K. J., Carneiro, L., and Munro, D. S.: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome, 1965, Editors C. Cassano and M. Andreoli, Academic Press, New York, 1965, p. 455.
22. Kriss, J. P., Pleshakov, V., and Koblin, R.: Clin. Res., 12:116, 1964 (Abst.).
23. Nisonoff, A., Wissler, F. C., Lipman, L. N., and Woernley, D. L.: Arch. Biochem., 89:230, 1960.
24. Porter, R. R.: Biochem. J., 73:119, 1959.
25. McKenzie, J. M.: Program Am. Soc. Clin. Invest., April 1963, p. 48 (Abst.).
26. Kriss, J. P., Pleshakov, V., Rosenblum, A., and Chien, J. R.: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome, 1965, Editors C. Cassano and M. Andreoli, Academic Press, New York, 1965, p. 453.
- 26a. Volpe, R., Desbarats-Schonbaum, M. L., and Ezrin, C.: Program Am. Thyroid Assoc. Meeting, p. 77, 1967.
- 26b. McKenzie, J. M.: Physio. Rev., 48:1, 1968.
- 26c. Mannik, M., and Kunkel, H. G.: J. Exp. Med., 117:213, 1963.
- 26d. Kriss, J. P.: J. Clin. Endocr., in press (Oct. 1968).
- 26e. Miyai, K., Fukuchi, M., Kumahara, Y., and Abe, H.: J. Clin. Endocr., 27:855, 1967.
- 26f. Beall, G. N., and Solomon, D. H.: J. Clin. Endocr., 28:503, 1968.
27. Kriss, J. P., Pleshakov, V., Rosenblum, A., and Chien, J. R.: Vth Pan American Congress of Endocrinology, Excerpta Medica International Congress Series No. 99, Abst. 53.
28. Fleischman, J. B., Pain, R., and Porter, R. R.: Arch. Biochem. Biophys., Suppl. 1, 174, 1962.
29. Criddle, R. S.: Arch. Biochem. Biophys., 106:101, 1964.
30. Dorrington, K. J., Munro, D. S., and Carneiro, L.: Lancet, 2:889, 1964.
31. McKenzie, J. M.: Trans. Assoc. Am. Phys., 78:174, 1965.
32. McKenzie, J. M., and Gordon, J.: Program 47th meeting of the Endocrine Society, 1965, Abst. 6.
33. Lepp, A., and Oliner, L.: Endocrinology, 80:369, 1967.
34. Pinchera, A., Pinchera, M. G., and Stanbury, J. B.: J. Clin. Endocr., 25:189, 1965.
35. Beall, G. N., and Solomon, D. H.: J. Clin. Invest., 45:552, 1966.
36. Beall, G. N., and Solomon, D. H.: Clin. Research, 14:174, 1966 (Abst.).
37. Dorrington, K. J., Carneiro, J., and Munro, D. S.: J. Endocr., 34:133, 1966.
38. El Kabir, D. J., Benhamou-Glynn, N., Doniach, D., and Roitt, I. M.: Nature, 210:319, 1966.
39. Adams, D. D., and Kennedy, T. H.: J. Clin. Endocr., 27:173, 1967.
40. Burke, G.: J. Lab. Clin. Med., 69:713, 1967.
41. Pinchera, A., Liberti, P., and Badalamenti, F.: Lancet, 1:374, 1966.

42. Solomon, D. H., and Beall, G. N.: Clin. Res., 15:127, 1967 (Abst.).
43. Blum, S., Hargardine, J. R., and Greenspan, F. S.: Clin. Res.: 15:122, 1967, (Abst.).
44. McKenzie, J. M.: Meeting Am. Soc. Clin. Invest., May, 1966 Abst. 73.
45. Burke, G.: J. Clin. Endocr., 27:1095, 1967.
46. Shishiba, Y., Solomon, D. H., and Beall, G. N.: Clin. Res. 15:99, 1967 (Abst.).
47. Scott, T. W., Good, B. F., and Ferguson, K. A.: Endocrinology, 79:949, 1966.
48. Field, J. B., Remer, A., Bloom, G., and Kriss, J. P.: Meeting of American Society for Clinical Investigation, 1967 (Abst.).
49. Adams, D. D., and Kennedy, T. H.: J. Clin. Endocr., 25:571, 1965.
50. Racadot, J., Peillon, F., Sabaoun, J., and Gilbert-Dreyfus: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome 1965, Editors C. Cassano and M. Andreoli, Academic Press, New York, 1965, p. 593.
52. Astwood, E. B.: Advances Int. Med., 3:237, 1949.
53. Utiger, R. D.: J. Clin. Invest., 44:1277, 1965.
54. Odell, W. D., Wilber, J. F., and Paul, W. E.: J. Clin. Endocr., 25:1179, 1965.
55. Lemarchand-Beraud, Th., and Vannotti, A.: In Current Topics in Thyroid Research, Proceedings of the 5th International Thyroid Conference, Rome, 1965, Editors C. Cassano and M. Andreoli, Academic Press, New York, 1965, p. 527.
56. D'Angelo, S. A.: J. Clin. Endocr., 23:229, 1963.
57. Fajans, S. S., J. Clin. Endocr., 18:271, 1958.
58. Werner, S. C., and Stewart, W. B.: J. Clin. Endocr., 18:266, 1958.
59. Gurling, K. J., Baron, D. N., and Smith, E. J. R.: J. Clin. Endocr., 19:717, 1959.
60. McCullagh, E. P., Reynolds, C. W., and McKenzie, J. M.: J. Clin. Endocr., 20:1029, 1960.
61. Adams, D. D.: Brit. Med. J., 1:1015, 1965.
62. Kriss, J. P., Pleshakov, V., Rosenblum, A. L., Holderness, M., Sharp, G., and Utiger, R.: J. Clin. Endocr., 27:582, 1967.
63. Carneiro, L., Dorrington, K. J., and Munro, D. S.: Clin. Sci. 31:215, 1966.
64. Carneiro, L., Dorrington, K. J., and Munro, D. S.: Lancet, 2:878, 1966.
65. Noguchi, A., Kurihara, H., and Sato, S.: J. Clin. Endocr., 24:160, 1964.
66. McKenzie, J. M.: Program, Meeting of the Endocrine Society, June, 1963, p. 13 (Abst.).
67. Mosier, H. D.: J. Clin. Endocr., 25:1005, 1965.
68. McKenzie, J. M.: J. Clin. Endocr., 26:779, 1966.
69. Purves, H. D., and Adams, D. D.: In Thyrotropin, editor S. C. Werner, Charles C Thomas, Springfield, 1963, p. 281.
70. McKenzie, J. M.: J. Clin. Endocr., 25:424, 1965.
71. Liddle, G. W., Heyssel, R. M., and McKenzie, J. M.: Am. J. Med., 39:845, 1965.
72. Major, P. W., and Munro, D. S.: J. Endocr., 20:XIX (Proceedings), 1960 (Abst.).
73. Rosenberg, D., Grand, M. J. H., and Silbert, D.: New Eng. J. Med., 268:292, 1963.
74. McKenzie, J. M.: J. Clin. Endocr., 24:660, 1964.
75. Sunshine, P., Kusumoto, H., and Kriss, J. P.: Pediatrics, 36:869, 1965.
76. Holmes, R. A., Engring, N. H., and Engstrom, W. W.: Ann. Int. Med., 62:1008, 1965.
77. Vahlquist, B.: Advances Pediat., 10:305, 1958.
78. Margetts, B. M. (for M. J. Wilmers): Proc. Roy. Soc. Med., 43:615, 1950.
79. Fischer, P. M. S.: S. Afr. Med. J., 25:217, 1951.
80. Riley, I. D., and Sclare, G.: Brit. Med. J., 1:979, 1957.
81. Glass, S. D., Townsley, J. T., and Geppert, L. J.: J. Pediat., 64:906, 1964.
82. Snyder, M. J., Green, D. E., and Solomon, D. H.: J. Clin. Endocr., 24:1129, 1964.
83. Gitlin, D., Kumate, J., Urrusti, J., and Morales, C.: Nature, 203:86, 1964.
84. Mahoney, C. P., Pyne, G. E., Stamm, S. J., and Bakke, J. L.: Am. J. Dis. Child., 107:516, 1964.
85. Adams, D. D., and Purves, H. D.: Metab. 6:26, 1957.
86. Werner, S. C.: Clin. Sci., 177:551, 1961.
87. Pimstone, B. L., Hoffenberg, R., and Black, E.: J. Clin. Endocr., 24:976, 1964.
88. Solomon, D. H., Green, D. E., Snyder, M. J., and Nelson, J. C.: Clin. Res., 12:119, 1964.
89. Irvine, W. J.: Quart. J. Exp. Physiol., 49:324, 1964.
90. Anderson, J. R., Gray, K. G., Middleton, D. G., and Young, J. A.: Brit. J. Med. 2:1930, 1964.
91. McEachern, D., and Parnell, J.: J. Clin. Endocr. 8:842, 1948.
92. Levy, G., Meadows, W. R., and Gunnar, R. M.: Ann. Int. Med., 35:134, 1951.
93. Goldstein, Gideon: Personal communication.
94. McKenzie, J. M.: Program, Meeting Am. Thyroid Assoc., Chicago, 1966, p. 44 (Abst.).
95. Wyse, E. P., McConahey, W. M., Woolner, L. B., Scholtz, D. A., and Kearns, T. P.: Program, Meeting Am. Thyroid Assoc., Chicago, 1966, p. 46 (Abst.).
96. Perloff, W. H.: J. Clin. Endocr., 16:542, 1956.
97. Catz, B., Perzik, S. L., and Bauer, F. K.: Clin. Res. 14:176, 1966 (Abst.).
98. Catz, B.: Clin. Res., 15:122, 1967 (Abst.).
99. Werner, S. C., Feind, C. R., and Aida, M.: New Eng. J. Med., 276:132, 1967.
100. Webster, B., Johnston, M. W., Schonbaum, E., and Volpe, R.: Meeting Endocrine Society, June, 1963, Abst. 179.
101. Kriss, J. P., Pleshakov, V., Rosenblum, A., and Sharp, G.: J. Clin. Endocr., 27:59, 1967.
102. Edmundowicz, A. C., Ivy, H. K., and Randall, R. V.: Postgrad. Med., 35:600, 1964.
103. Chremos, A. N.: Am. J. Med., 38:954, 1965.
104. Grynkwich, S. E., Laughlin, R. M., Herron, F. T., and Carmel, Jr., W. J.: Amer. J. Med. Sci., 222:142, 1951.
105. Beierwaltes, W. H.: Ann. Int. Med., 40:968, 1954.
106. Faikow, P. J.: Amer. J. Human Genetics, 18:93, 1966.
107. Burgio, G. R., Severi, F., Rossoni, R., and Vaccaro, R.: Lancet, 1:166, 1965.
108. McGirr, E. M., and Murray, I. P. C.: J. Clin. Endocr., 16:160, 1956.
109. Johnson, J. E., and Cook, A. R.: J. Clin. Endocr., 22:665, 1962.
110. Meek, J. C., and Vanderlaan, W. P.: Clin. Res., 12:92, 1964 (Abst.).
111. Snyder, N. J., Green, D. E., and Solomon, D. H.: J. Clin. Endocr., 24:1129, 1964.
112. Blizzard, R. M., Hung, W., Chandler, R. W., Aceto, Jr., T., Kyle, M., and Winship, T.: New Eng. J. Med. 267:1015, 1962.
113. Werner, S. C., and Platman, S. R.: Lancet, 2:751, 1965.
114. Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W.: J. Clin. Endocr., 10:1375, 1950.
115. Wikholm, G., and Einhorn, J.: J. Clin. Endocr., 23:76, 1963.
116. Brochner-Mortensen, K.: Acta Med. Scan., 121:171, 1945.
117. Brunn, E.: Acta Med. Scan., 122:13, 1945.
118. Brain, W. R.: Lancet, 1:182, 1936.
119. Lous, P.: Acta Med. Scan., 122:83, 1945.
120. Walzer, M.: J. Immunol., 14:143, 1927.
121. Ratner, B., and Gruebl, H. L.: J. Clin. Invest., 13:517, 1934.
122. Leissring, J. C., Anderson, J. W., and Smith, D. W.: Amer. J. Dis. Child., 103:160, 1962.
123. Schwartz, M.: Lancet, 2:1200, 1958.
- 123a. Dymling, J. F., and Becker, D. V.: J. Clin. Endocr., 27:1487, 1967.
124. Falconer, I. R., and Hetzel, B. S.: Endocrinology, 75:42, 1964.
125. Hetzel, B. S., de la Haba, D. S., and Hinkle, Jr., L. E.: J. Clin. Invest., 31:638, 1952.
126. Volpe, R., Vale, J., and Johnston, M. W.: J. Clin. Endocr., 20:415, 1960.
127. Utiger, R. D.: J. Clin. Invest. 44: 1277, 1965.
128. Odell, W. D., Wilber, J. F., and Paul, W. E.: J. Clin. Endocr., 25:1179, 1965.

CASE REPORTS

Sequential Hepatic Alterations Resulting From Hepatic Duct Obstruction

S. L. NIELSEN, M.D., AND E. L. KEHOE, M.D.,
San Francisco

NUMEROUS CASES OF adenocarcinoma of the hepatic ducts are recorded in the medical literature. However, few emphasize the pathological status of the liver and, more particularly, the different stages of biliary obstruction that can occur within the same liver. A case is reported herein in which the pathologic changes in the liver were monitored and showed sequential changes as a result of obstruction due to adenocarcinoma of the hepatic ducts in the porta hepatis.

Report of a Case

A 49-year-old white woman was admitted to San Francisco General Hospital 27 November 1966 because of jaundice, weakness, fatigue and confusion.

Medical History. The patient was unable to give a history. The daughter stated that the patient had been in good health until, three or four months before admission, she became depressed because

of loss of a job, and weakness and fatigue then gradually developed. A private physician prescribed a variety of drugs including multiple vitamin preparations, digitalis, thyroid extract and chlorothiazide for mild hypertension (160/90 mm of mercury). In late October 1966, a preparation containing amphetamine and prochlorperazine was prescribed for extreme fatigue and lethargy. One week later the stools were clay colored and the urine was dark brown. Icterus was first noted by the physician on 4 November 1966. There was no nausea, vomiting, abdominal pain or anorexia. The patient refused advice to enter a hospital. Jaundice became more severe, lethargy became more pronounced, and pedal edema developed. Chlorothiazide therapy, which had been discontinued, was resumed. The patient became stuporous and confused three days before admission to hospital.

The only past history of a hepatic disorder was a mild attack of hepatitis with jaundice 20 years earlier. It subsided within three or four weeks and symptoms did not recur. The patient did not consume alcohol excessively, was not addicted to drugs, and did not use hepatotoxic cleaning agents.

Physical Examination. The patient was jaundiced, confused, lethargic and uncooperative. Vital signs were within normal limits. The blood pressure was 120/80 mm of mercury. Pertinent physical findings were essentially those associated with hepatic disease. The edge of the liver was palpable 8 cm below the right costal margin. The right lobe was firm and smooth but the left lobe was rocky, hard and nodular. Ascites was evident and the tip of the spleen was not felt. Palmar erythema was noted, and there were a few spider angiomas scattered over the chest and upper arms.

The patient was considered to have severe liver disease and to be in a hepatic precoma. Biliary cirrhosis, secondary to intra- or extrabiliary tract obstruction, or postnecrotic cirrhosis, with or with-

From the Pathology and Medical Services, San Francisco General Hospital, University of California School of Medicine, San Francisco.

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Reprint requests to: Editorial Office, Medical Services, San Francisco General Hospital, 22nd Street and Potrero Avenue, San Francisco, California 94110 (Dr. Kehoe).

TABLE 1.—*Pertinent hematologic data*

<i>Hospital day</i>	<i>Hematologic values</i>					<i>Results of serum analysis</i>					
	<i>Packed cell volume</i>	<i>White blood cell count</i>	<i>Prothrombin time</i>	<i>Total proteins</i>	<i>Albumin</i>	<i>Globulin</i>	<i>Serum glutamic pyruvic transaminase</i>	<i>Serum lactic dehydrogenase</i>	<i>Total bilirubin</i>	<i>Direct bilirubin</i>	<i>Alkaline phosphatase</i>
	<i>per 100 ml</i>	<i>per cu mm</i>	<i>% of normal</i>	<i>gm/100 ml</i>	<i>gm/100 ml</i>	<i>gm/100 ml</i>	<i>units</i>	<i>units</i>	<i>mg/100 ml</i>	<i>mg/100 ml</i>	<i>S.J.R. units</i>
Pre operative											
1	41	10,000	56	6.5	1.4	5.1	.98	152	33.6	21.2	5.3
12	38	8,900	49	6.5	2.0	4.5	138	130	37.8	26.0	6.7
During surgery											
23											
24	42	14,900	52	5.6	2.0	3.6	258	750	36.0	25.6	8.3
30	43	15,300	—	4.7	0.5	4.2	102	130	22.8	14.0	5.4
38	28	12,100	56	3.7	0.8	2.9	—	—	17.2	12.8	—
40	32	10,900	—	4.3	0.9	3.4	—	—	21.6	18.0	—

out primary malignant disease of the liver, were considered the most likely diagnostic possibilities.

Course. Diagnostic studies were carried out to determine the cause of jaundice (Table 1). The prothrombin time was low, as was the concentration of total serum proteins, and the albumin:globulin ratio was reversed. These results together with spider angiomas and palmar erythema suggested severe hepatocellular disease. The level of alkaline phosphatase was slightly elevated and the direct serum bilirubin value was high.

On 2 December 1966, percutaneous needle biopsy of the right lobe of the liver was performed. The tissue showed characteristic changes of extrahepatic biliary obstruction¹ with prominent cholestasis, slight to moderate portal fibrosis, bile "infarcts" and minimal necrosis of hepatic cells.

On 12 December a scintiscan of the liver using Au¹⁹⁸ and biliary excretion studies employing Rose Bengal I¹³¹ were performed. Hepatic I¹³¹ uptake was decidedly decreased and multiple small space-occupying lesions in the liver and splenomegaly were present.

On 15 December, a percutaneous transhepatic cholangiogram was obtained. The dorsocaudal portion of the right intrahepatic ductal system was grossly dilated but no contrast media entered the ventrocranial portion. Percutaneous needle biopsy of the left lobe of the liver was performed. As no bile could be aspirated from the anterior extrahepatic portion of the biliary ductal system to the left lobe, contrast material was not injected. It was concluded that obstruction of the dorsocaudal portion of the right intrahepatic biliary ductal system was complete and far advanced, and that a mass was present in the left lobe of the liver which

obstructed passage of contrast material into the biliary radicles of this lobe.

On the basis of these studies, the persistent jaundice, and the progressive deterioration of the patient, exploratory laparotomy was performed on 20 December. During the operation, 750 ml of clear yellow ascitic fluid was removed from the bile-stained peritoneal cavity. The liver was considerably enlarged and the right and left lobes differed considerably in appearance and consistency: the right lobe was firm, smooth and of greenish hue; the left lobe was nodular, very hard, and light yellow-brown. Biopsy specimens were obtained. An irregular mass, 5 x 5 cm and rock hard, was palpated at the porta hepatis; a biopsy specimen was obtained. The gallbladder and the cystic and common bile ducts looked normal and no calculi were felt. Portal hypertension was evidenced by large dilated veins of the greater omentum and splenic hilus. To reduce the jaundice, the obstructed area of the porta hepatis was by-passed by establishing a communication between the posterior wall of the gallbladder and the dilated intrahepatic right biliary ductal system. Cholecystostomy was performed with external drainage through a Foley catheter. Cholangiography during the operation showed free flow of contrast material from the dilated right intrahepatic bile ducts into the gallbladder and into the duodenum by way of the patent cystic and common bile ducts.

Postoperatively, the level of serum bilirubin decreased moderately but the clinical status of the patient continued to deteriorate: fever and disturbances in electrolyte balance developed and persisted in spite of corrective efforts.

The patient died on the seventeenth postoperative day and autopsy was performed.

Pathological Findings. Examination of hepatic tissue from the right lobe, obtained by percutaneous needle biopsy on 2 December revealed prominent cholestasis with characteristic areas of pseudoxanthomatous change, isolated acidophilic cells indicating necrosis of parenchymal cells, and slight to moderate portal fibrosis; all indicated extrahepatic biliary obstruction. Examination of hepatic tissue from the left lobe, obtained by percutaneous needle excision 13 days after the first specimen, indicated considerable disruption of the hepatic architecture by extensive fibrosis and numerous proliferating bile ducts. Only small groups of hepatocytes, exhibiting prominent cholestasis, remained. Cholestasis was both intracellular and intracanalicular. These results indicated advanced active biliary cirrhosis.

Examination of the wedges of tissue obtained from different areas of the liver during operation revealed the following: The only abnormality in tissue from the right lobe was bile stasis with no evidence of disruption of architecture. Tissue from the left lobe showed the parenchyma almost completely replaced by proliferating bile ductules encased in an extensive fibrous stroma, although portal areas were still identifiable, small groups of

hepatocytes with intracellular cholestasis surrounded the central veins, and numerous intracanalicular bile plugs with an extensive inflammatory cellular response surrounded the proliferating bile ducts. Tissue from the tumor revealed a stroma composed of relatively acellular collagenous connective tissue containing numerous small irregular glands and ducts composed of malignant epithelial cells of the low cuboidal type with large hyperchromatic atypical nuclei and frequent mitotic forms.

Gross and microscopic findings during autopsy were as follows. The liver weighed 1,700 gm. The most striking abnormality was the yellowish white tumor, which was 5 cm in diameter and rock hard, in the porta hepatis adjacent to the inferior vena cava (Figure 1). A probe was passed 2 to 3 mm into the right hepatic duct, via the opened common hepatic duct, before encountering the obstructing tumor, and could not be passed into the left hepatic duct as it was entirely filled with tumor. The left hepatic lobe was small, nodular, firm and green. The right lobe was fairly soft, particularly at the dome, and green. A cross-section revealed considerable dilation of the ductal system. The extreme lateral portion was fibrotic, non-nodular and pale yellow, in contrast with the dark green soft medial portion (Figures 2 and 3).

The gallbladder was 4 cm long and showed a well healed surgical scar 2 cm long. Cholecystostomy with a Foley catheter drain to the external abdominal wall was present. Inside, the mucosa was velvety and bile-stained. The fistula extended through the posterior wall into the dilated right

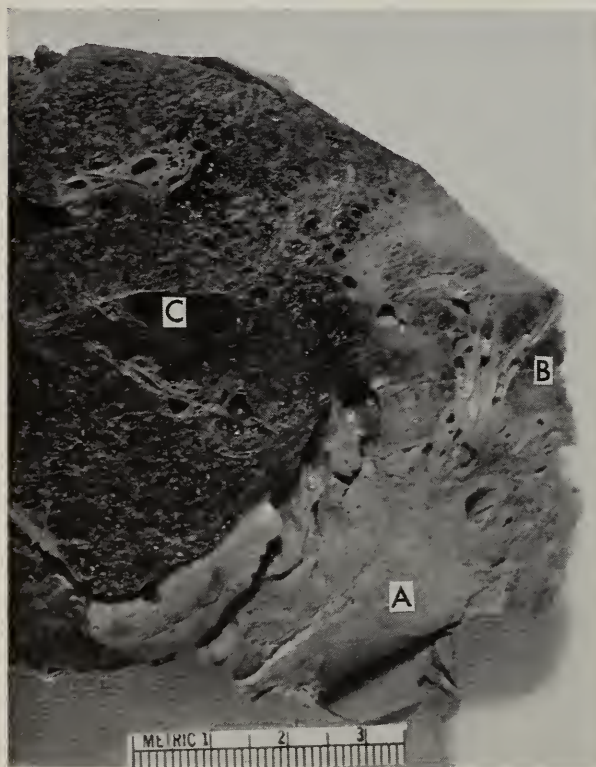


Figure 1.—A section through the area of the porta hepatis showing the gross features of the tumor (A), a small portion of the fibrotic left lobe (B) and details in the medial right lobe (C).

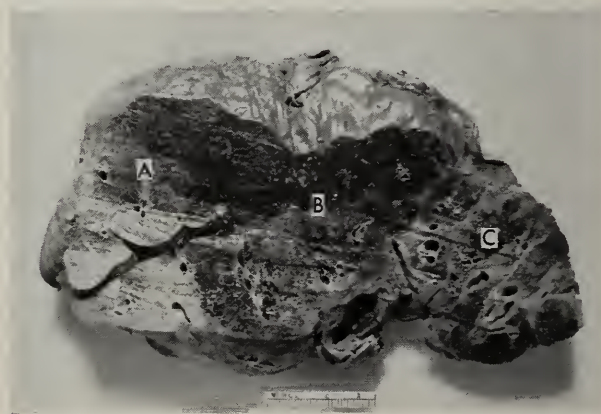


Figure 2.—Cross-section of the liver showing three distinct changes—from left to right, early cirrhosis of the lateral portion (A) sharply demarcated from the soft cystic medial portion of the right lobe (B), and the left lobe with broad bands of fibrous tissue (C). (Note: the cystic change is due in part to postmortem growth of Gram-positive rods, and in part to dilated bile ducts.)



Figure 3.—A deeper section of the right lobe, showing the distinct morphologic variation between the two portions.

hepatic ductal system and was anatomically patent, as were the cystic and common bile ducts.

Microscopically, tissue from sections through the extreme lateral portion of the right lobe of the liver showed severe portal fibrosis with decided proliferation of bile ductules, cholestasis and numerous "bile infarcts." There was portal-to-portal bridging with a few areas of portal-to-central bridging. The centrilobular areas were severely necrotic (Figure 4). In sharp contrast to and clearly demarcated from the lateral portion of the right lobe the medial portion showed marked cholestasis and "bile infarcts," but no proliferation of bile ductules or increase in fibrosis connective tissue. Sections of the left lobe showed biliary cirrhosis with only a few groups of hepatocytes scattered within the dense fibrous connective stroma (Figure 5). Only a few bile ductules were present in the fibrous septae. Sections of the tumor

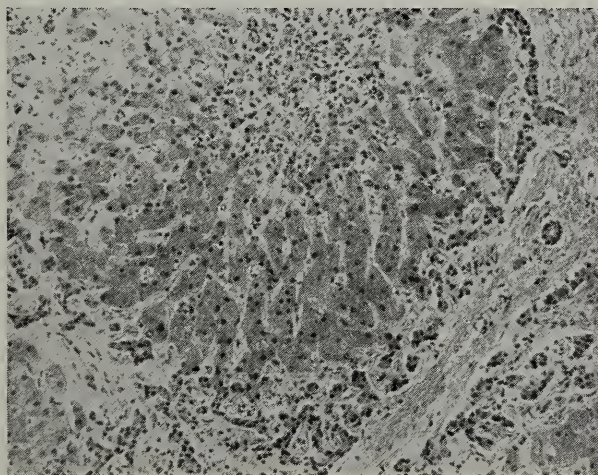


Figure 4.—Photomicrograph of tissue from the lateral right lobe, showing the edge of a nodule with cholestasis, bile ductule proliferation and scarring (original magnification X 100).

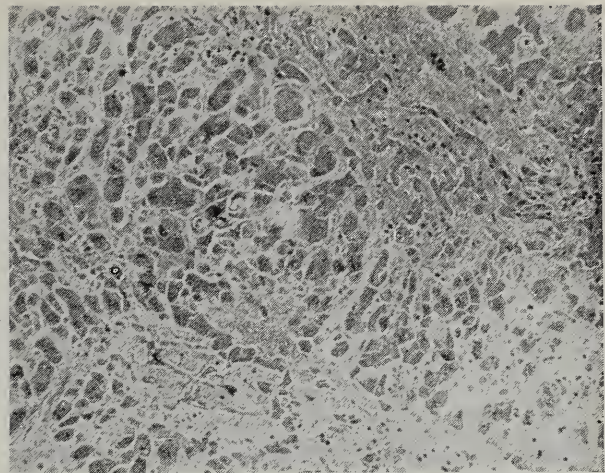


Figure 5.—Photomicrograph of tissue from the left lobe, showing broad bands of fibrous connective tissue and cholestasis but insignificant ductule proliferation (original magnification X 100).

were identical with those obtained for biopsy during operation (Figure 6).

Other postmortem findings were as follows. A blood culture produced a heavy growth of *Klebsiella aerogenes*. A culture of lung tissue showed no bacterial growth. Hashimoto's thyroiditis was present in the thyroid gland and a calcified lesion of empyema containing caseous material was present in the left pleural space. In addition, there were caseating granulomas in the left upper lobe of the lung. No acid-fast bacilli were detected by smear, culture or on tissue section.

The final anatomic diagnosis was adenocarcinoma of the hepatic bile ducts with far-advanced biliary cirrhosis of the left hepatic lobe, active but less severe biliary cirrhosis of the lateral portion

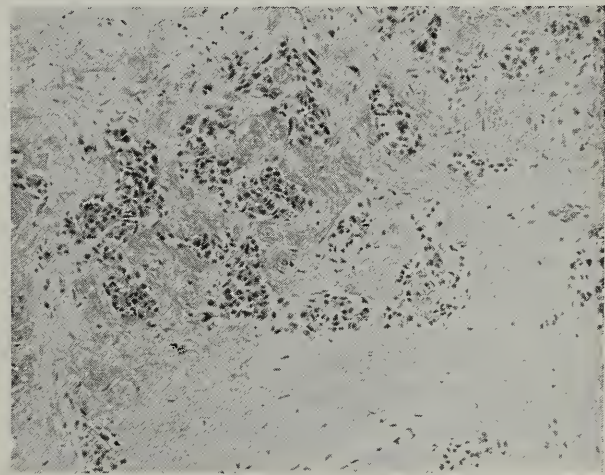


Figure 6.—Photomicrograph of the adenocarcinoma, showing the dense stroma surrounding the irregular clusters of malignant ductal cells (original magnification X 100).

of the right lobe, and cholestasis but not cirrhosis of the medial right hepatic lobe.

Discussion

The three distinct pathological features in the liver of this patient strikingly illustrate the consequences of progressive biliary obstruction. The hepatic changes lead us to speculate on the natural history of the ductal malignant changes: The far-advanced stage of biliary cirrhosis present in the left lobe indicates the left hepatic duct was obstructed initially by the tumor. Eventually, the expanding growth occluded branches of the right hepatic draining the lateral portion of the right lobe, probably explaining the less severe but more active biliary cirrhosis present in that area of the lobe. Finally, the tumor invaded and occluded the remaining branches of the right hepatic duct, causing pronounced cholestasis but no cirrhosis in the medial portion of the right lobe.

More precisely, the time of onset of obstruction in the various portions of the hepatic lobes according to the histologic changes is purely conjecture. However, from observations reported by others, certain generalizations can be made. Shorter and Baggenstoss² studied the histologic changes produced by extrahepatic biliary obstruction in 71 patients. The only changes in hepatic appearance that followed a chronologic sequence were in the structures of the connective tissue. After onset of jaundice, fibroblastic proliferation occurred in the portal tracts within seven days, and nodular regeneration of hepatic parenchyma as early as 212 days. However, cirrhosis was not established for at least 400 days. Scobie and Summerskill³ analyzed 457 histories of patients with biliary cirrhosis seen at the Mayo Clinic from 1950 through 1962. The mean time interval between onset of biliary obstruction and confirmation of biliary cirrhosis varied widely according to the cause of obstruction: 0.8 years (ranging from 0.2 to 1.5 years) for patients with obstructing malignant disease; 7.1 years for patients with stricture of the common duct; and 4.6 years for patients with common duct calculi.

According to these time intervals, the presence of far-advanced biliary cirrhosis in the left lobe of the patient in the present case indicates the left hepatic duct was obstructed for at least two and a half months and probably much longer. The presence of cholestasis and absence of cirrhosis and fibroblastic response in the medial portion of the

right lobe indicate fairly recent blockage of the right hepatic duct. The active cirrhotic process present in the lateral portion of the right lobe was a relatively recent development, probably between one and two and a half months. Since the initial biopsy of the left lobe was performed five weeks after onset of clinical jaundice, the advanced degree of cirrhosis present indicates that the left hepatic duct was obstructed for some time before the onset of jaundice.

Schalm and coworkers⁴ showed experimentally that ligation of one hepatic duct does not cause jaundice until the flow of bile in the opposite duct is also impaired. Indirectly, this is evidenced in patients with jaundice resulting from adenocarcinoma of the bile ducts when diversion, curettage, or cannulation of the obstructed duct effects prompt subsidence of jaundice.⁵⁻⁸ Schalm's observations are challenged by investigators who report that unilateral obstruction of a hepatic duct can cause jaundice, implying that the remaining parenchyma of normal liver cannot clear the circulating conjugated bilirubin.⁹ The sequence of events in the present case supports the observation of Schalm⁴—namely, that jaundice does not occur until both hepatic ducts are occluded. We believe that the left hepatic duct in our patient was blocked for a considerable time before jaundice appeared, and that it was not until the tumor encroached upon the right hepatic duct that icterus developed.

One interesting but unexplainable feature is the high bilirubin value that accompanied the slightly elevated level of alkaline phosphatase. This finding supports the observation of VanHeerden and coworkers¹⁰ that these two values can be variable and therefore not diagnostic in patients with malignant obstruction of the hepatic ducts. This may be kept in mind as a caveat when recalling the classic teaching that a high level of alkaline phosphatase and a slight increase in the serum bilirubin usually mean an obstructing carcinoma.

Recently, Klatskin⁷ reviewed the clinical course of patients with adenocarcinoma of the hepatic bile ducts; as did the patient in the present case, 11 of his 13 patients died of progressive hepatocellular failure, and in eight out of the 13 patients metastasis did not occur. Palliative operation with diversion of the bile flow or curettage in patients with a papillary tumor may prolong survival. Early recognition of intrahepatic ductal tumors requires early suspicion, proper interpretation of results of liver function studies and the judicious

use, as circumstances indicate, of liver biopsy and percutaneous transhepatic cholangiography.

Summary

A case of adenocarcinoma of the hepatic ducts within the porta hepatis, producing three distinct stages of biliary obstruction in the liver, is reported. The natural history of this tumor and the development of jaundice after unilateral hepatic duct occlusion is discussed on the basis of the sequential changes observed.

REFERENCES

1. Gall, E. A., and Dobrogorski, O.: Hepatic alterations in obstructive jaundice, *Amer. J. Clin. Path.*, 41:126-139, Feb. 1964.
2. Shorter, R. G., and Baggenstoss, A. H.: Extrahepatic cholestasis: histologic features, *Amer. J. Clin. Path.*, 32:1-17, July 1959.
3. Scobie, B. A., and Summerskill, W. H. J.: Hepatic cirrhosis secondary to obstruction of the biliary system, *Amer. J. Dig. Diseases*, 10:135-146, Feb. 1965.
4. Schalm, L., Bax, H. R., and Mansens, B. J.: Atrophy of the liver after occlusion of the bile ducts or portal vein and compensatory hypertrophy of the unoccluded portion and its clinical importance, *Gastroenterology*, 31:131-155, Aug. 1956.
5. Klataskin, G.: Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis, *Amer. J. Med.*, 38:241-256, Feb. 1965.
6. Alvarez, A. F.: Carcinoma of the main hepatic ducts within the liver, *Ann. Surg.*, 148:773-782, Nov. 1958.
7. Meyerowitz, B. R., and Aird, I.: Carcinoma of the hepatic ducts within the liver, *Brit. J. Surg.*, 50:178-184, Sept. 1962.
8. Thorbjarnarson, B.: Carcinoma of intrahepatic bile ducts, *Arch. Surg.*, 77:908-917, Dec. 1958.
9. Mistilis, S., and Schiff, L.: A case of jaundice due to unilateral hepatic duct obstruction, with relief after hepatic lobectomy, *Gut*, 4:13-15, March 1963.
10. VanHeerden, J. A., Judd, E. S., and Dockerty, M. D.: Carcinoma of the extrahepatic ducts, *Amer. J. Surg.*, 113:49-56, Jan. 1967.

Acute Promyelocytic Leukemia With Hypofibrinogenemia

WILLIAM C. LAWS, A.B.*,

RICHARD A. BOHANNON, M.D.,

A. JEAN ROBINSON, PH.D., AND

PAUL M. AGGELER, M.D., *San Francisco*

THE SYNDROME OF acute promyelocytic leukemia with hypofibrinogenemia, first described by Croizat and Favre-Gilly in 1949,¹ is characterized by low plasma fibrinogen, thrombocytopenia, and a fulminant clinical course terminating in fatal hemor-

rhage. Approximately 55 cases have been reported. A similar bleeding disorder has been associated, rarely, with myeloblastic leukemia² and chronic myelogenous leukemia in blastic transformation.³

The following case reported documents further the syndrome and presents additional data regarding the pathogenesis of the bleeding diathesis.

Report of a Case

A 46-year-old Japanese man was healthy until four days before admission to Children's Hospital, when patches of ecchymosis developed on the lower extremities. Similar lesions appeared on the trunk, arms and groin. The patient was admitted 28 June 1967 because of prolonged facial bleeding after shaving. The medical history revealed no recent malaise, anorexia, weight loss, fever, chills, melena or hematuria, and no known exposure to toxic drugs or chemicals. Neither the patient nor the family had a history of blood dyscrasia.

Physical examination showed a well developed and well nourished patient in no distress. Multiple ecchymotic areas 5 to 10 cm in diameter were present on the arms, trunk, groin and legs, and there were a few petechiae on the right forearm. The blood pressure was 102/70 mm of mercury, the pulse 92 per minute and the temperature 36.7°C (98°F). Scleral icterus was not present, mucous membranes were slightly pale, and several petechiae were present on the palate. A few barely palpable nodes along the right posterior cervical chain were noted but no other lymph nodes were felt. No sternal or rib tenderness was elicited. The liver and the spleen were not enlarged on palpation. All other results of physical examination were within normal limits.

Results of initial hematologic tests were as follows: red blood cell count, 4.07 million per cu mm; hemoglobin, 12.8 gm per 100 ml; hematocrit, 34 percent; white blood cell count, 5,600 per cu mm; differential leukocyte count, 36 percent lymphocytes, 24 percent neutrophils, 3 percent band forms, 2 percent metamyelocytes, 30 percent promyelocytes and 5 percent myeloblasts; and platelet count, 8,100 per cu mm. Urinalysis showed a specific gravity of 1.029 and no glucose, ketones or protein. Rare crenated erythrocytes were present in the urinary sediment. Bone marrow aspirate showed extensive infiltration by immature granulocytic elements, with 84 percent promyelocytes and 10 percent myeloblasts. No erythroid precursors or megakaryocytes were seen. The Lee-White clot-

*Student Oncology Trainee, University of California School of Medicine, supported by U.S. Public Service Health Grant 1 T12 CA 8054-01.

From the Medical Services, San Francisco General Hospital, University of California School of Medicine, and Children's Hospital, San Francisco. This work was supported in part by grants TI AM-5103, HE-02754, and IK 6 HE-21,835 from the U.S. Public Health Service.

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Reprint requests to: Hematology Research Laboratory, Children's Hospital and Adult Medical Center, 3700 California Street, San Francisco 94118 (Dr. Bohannon).

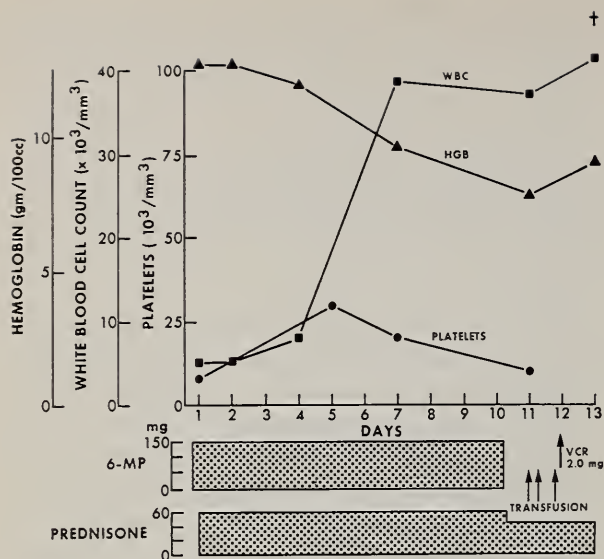


Chart 1.—Summary of clinical course and treatment.

ting time was 9 minutes and the clot was small and friable. The one-stage prothrombin time was 33 percent and the thrombin time was prolonged to 33.8 seconds (normal 12 seconds). The fibrinogen concentration was 117 mg per 100 ml. Other coagulation tests are described under the heading *Special Studies*.

A diagnosis of acute promyelocytic leukemia was made and therapy with 6-mercaptopurine (6-MP) (Purinethol®), 150 mg, and prednisone, 60 mg, daily was begun.

The disease was stable until day 9, when fresh patches of ecchymosis appeared and weakness and dyspnea occurred. Serial blood counts showed moderate anemia and progression of leukemia (Chart 1). On day 11, 3 units of packed red blood cells were administered; 6-MP was discontinued and vincristine sulfate (Oncovin®), 2.0 mg, was administered intravenously. Prednisone therapy was reduced to 40 mg a day. On day 13 two episodes of massive hematemesis occurred and the patient quickly became moribund, with stupor and quadriplegia. Massive areas of ecchymosis were present on the right forearm and hand and the left flank and buttock, and there were numerous smaller patches on both arms and legs. Funduscopic examination showed fresh extensive bilateral splotchy retinal hemorrhages. The patient became comatose and died.

Autopsy revealed extensive purpura. Many petechiae were present on the visceral pericardium and serosa of the small bowel. The heart, lungs, liver and kidneys were normal. The spleen weighed 220 gm. No ulcerations were found in the gastro-

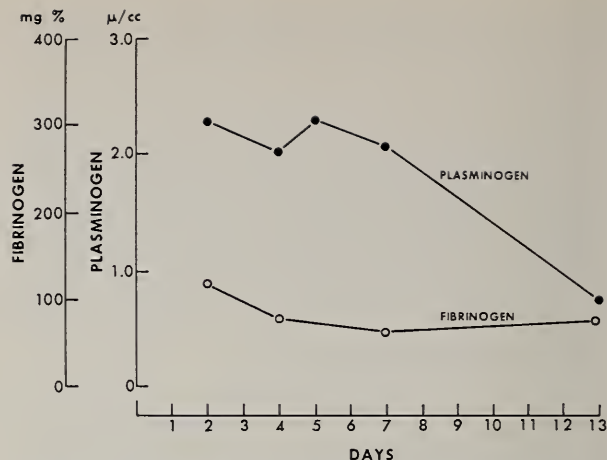


Chart 2.—Change in concentration of fibrinogen and plasminogen during clinical course.

intestinal tract. A large subarachnoid hemorrhage covered the entire right cerebral hemisphere; a large hematoma was present, involving the right hemisphere in the area of the rolandic sulcus and extending into the right lateral ventricle.

Microscopic examination demonstrated leukemic infiltration of the brain and spleen. Focal hemorrhage was seen in the brain, lungs, liver, spleen, and adrenal glands. The kidneys showed no abnormalities. Although an extensive search was made for intravascular fibrin thrombi, none was found.

The anatomical diagnosis was acute leukemia of the promyelocytic type, and death resulted from intracranial hemorrhage.

Special Studies

Specific clotting factors were measured as follows: Factor I (fibrinogen) by the method of Ratnoff and Menzie;⁴ Factor II (prothrombin) by the method of Owren and Aas;⁵ Factor V (proaccelerin) by the method of Borchgrevink, Pool, and Stormorken;⁶ Factor VII (proconvertin) by the method of Owren and Aas⁵ with the use of congenital proconvertin deficient plasma; Factor VIII (antihemophilic factor) by the method of Pool and Robinson;⁷ Factor IX (plasma thromboplastin component, P.T.C.—Christmas factor) by the method of Kropatkin, Hoag, and Aggeler;⁸ and Factor X (Stuart-Prower) by the method of Bachmann, Duckert, and Koller.⁹

Plasminogen activator was estimated by the fibrin plate method of Astrup and Müllertz,¹⁰ and plasminogen was determined by the method of Alkjaersig, Fletcher, and Sherry.¹¹ Fibrinolytic degradation products in serum were measured with the tanned red-cell hemagglutination immunoinhi-

TABLE 1.—Summary of Special Coagulation Studies

Test	Normal Value	2	4	5	Hospital Day 7	11	13
One stage prothrombin complex activity (% of normal)	70-100	26	26	19	20		
Thrombin time (seconds)	10-12	33.8	41.1		33.4		29.9
Plasma Factors							
I (mg/100 ml)	200-400	117	79		63		96
II (% of normal)	60-130	126	92		106		72
V "	60-140	55	43		23		10
VII "	70-140	102	105		112		80
VIII "	50-200	45	44		31		18
IX "	60-160	278	307	435	545		200
X "	65-140	85	53		46		16
Plasminogens (units/ml)	2-4	2.36	2.00	2.36	2.05		0.76
Fibrin plates (plasminogen activator) (mm ²)	no lysis	6	43				90
Fibrinolytic degradation products							
Fi Test (serum titer)	0	1:4	1:2	1:2	1:2	1:16	1:8
*TRCHII (mcg/ml)	< 8	32	32	32	32	64	64

*TRCHII = Tanned red-cell hemagglutination immuno-inhibition test.

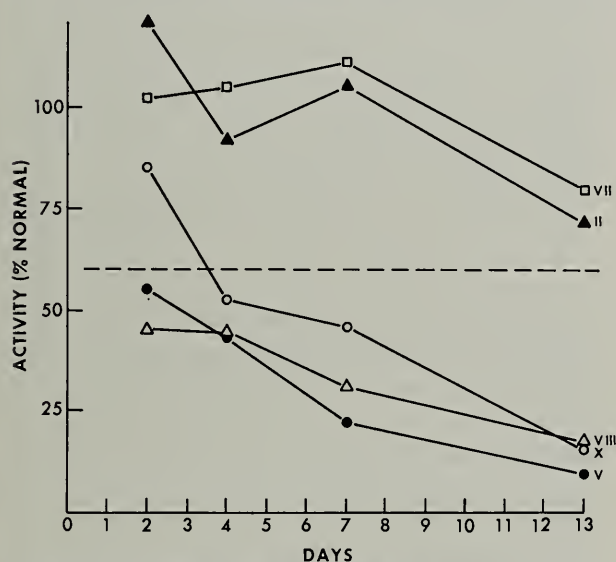


Chart 3.—Change in activities of Factors II, V, VII, VIII, and X during clinical course.

bition test (TRCHII)¹² and by the ability of the patient's serum to cause aggregation of latex particles coated with rabbit anti-human-fibrinogen antiserum (Fi Test reagent).*

The results are summarized in Table 1. The thrombin time, prolonged on admission, remained above twice the normal value throughout the clinical course. Similarly, the one stage prothrombin time (Quick) ranged between 19 and 26 percent. Fibrinogen concentration, initially 117 mg per 100 ml, decreased to less than 100 mg per 100 ml (Chart 2). The activity of Factors V and VIII was decreased in the initial specimens and con-

tinued to fall (Chart 3) to very low values. The concentration of Factor X, which was initially normal, also declined to a low level. The levels of Factors II and VII remained within the normal range. The activity measured in the Factor IX assay was far above normal and remained so throughout the clinical course. The euglobulin clot lysis time was 18 hours (normal is less than 2 hours) and the concentration of plasminogen was low but within normal limits until day 13 when it fell to 0.76 units per ml. Correspondingly, the concentration of plasminogen activator rose from the initial low level to a significantly high level in the final specimen. The serum titer of fibrinolytic degradation products, measured with rabbit anti-human fibrinogen serum, ranged between 1:4 and 1:16. A level of 32 to 64 micrograms per ml of fibrin degradation products was found in the TRCHII.* Terminally, the lysozyme activity of a random sample of urine was 33 grams per ml (normal is 0-2.5 grams per ml).

Comment

Acute promyelocytic leukemia with hypofibrinogenemia is distinguished from myeloblastic leukemia by several investigators.^{13,14} Patients with acute promyelocytic leukemia characteristically have a short fulminant clinical course, thrombocytopenia, and low levels of fibrinogen and Factor V. The patient reported herein had all of these features.

The syndrome is suspected when the blood and

*Fi Test reagent was supplied by Dr. Edward Shanbrom of the Hyland Laboratories, Los Angeles.

*We are grateful to Dr. Clarence Merskey, Albert Einstein College of Medicine, Bronx, N.Y., for these measurements.

marrow of a patient with acute granulocytic leukemia contain a high proportion of promyelocytes. The proportion of this cell type in the marrow is variable, ranging from 38 to 94 percent in the studies of Didisheim et al¹³ and of Rosenthal.¹⁴ These observers said that the finding of promyelocytes which contain morphologically atypical granules is more significant than the percentage of marrow promyelocytes. Results of coagulation screening tests which identify the syndrome include a low platelet count, decreased activity of the one-stage prothrombin time, and abnormal appearance of the clot which is typically small and friable.¹⁴

Few analyses of clotting factors in patients with the defibrination syndrome associated with acute promyelocytic leukemia are reported. Most observers have found a reduction in Factor V.¹³⁻¹⁶ In one case reported by Rosenthal, Factor X was reduced but Factor VIII was within normal limits.¹⁴ In five patients with acute leukemia or rhabdomyosarcoma, Merksey observed some reduction in Factors II, V, and VIII but little change in VII, IX, X, and XI.¹⁷ The pathogenesis of the bleeding diathesis of acute promyelocytic leukemia is the object of considerable interest. Early reports^{15,18} suggest fibrinolysis as the primary cause of hypofibrinogenemia, but confirmatory data are lacking and recent investigations do not support this concept.^{2,3,6,13,14}

Few studies conclusively document the more recent theory that intravascular coagulation is the cause of the bleeding disorder. However, the finding of a return to normal of the fibrinogen, Factor V and plasminogen concentrations during heparin therapy² strongly support it.

The low plasma concentrations of fibrinogen and of Factors V and VIII, the normal level of Factor II and the presence of fibrin degradation products in the present case is consistent with the diagnosis of either intravascular coagulation or primary fibrinolysis. The decreased levels of Factor X suggest disseminated intravascular clotting rather than fibrinolysis. The high level of activity in the Factor IX assay may represent the effect of circulating activated Factor X caused by disseminated intravascular coagulation, rather than an increase in the amount of Factor IX in the plasma. The failure of the clot to lyse during incubation for 24 hours, the normal initial level of plasma plasminogen, and the normal euglobulin clot lysis time exclude primary systemic activation of the fibrinolytic mechanism as the cause of the decreased con-

centration of clotting factors. Terminally, the concentration of plasma activator increased, as was indicated by a larger zone of lysis of the fibrin plate and the decreased concentration of plasminogen. This is best explained as secondary activation of the fibrinolytic mechanism consequent to primary intravascular coagulation.

The thrombin time was persistently prolonged, and although the titers were relatively low, fibrinolytic degradation products were found by immunologic testing on each of six occasions in the present case. Fletcher et al,¹⁹ Alkjaersig et al²⁰ and Nussenzweig et al²¹⁻²³ demonstrated that fibrinogen is degraded by plasmin into three classes of fragments with $S_{20,w}^0$ values of 5.27, 3.0 and a heterogeneous collection averaging 1.4. Nussenzweig et al^{21,22} established that the 5.27 S and 3.0 S fibrinogen fragments each possessed single distinctive antigenic determinants, which they designated D and E. Alkjaersig et al²⁰ found that only the 5.27 S fragment of fibrinogen inhibited the conversion, by thrombin, of fibrinogen to fibrin. The inhibitory action occurred through bonding of the fibrinogen fragment with fibrin monomer.

Definitive proof of the diagnosis of disseminated intravascular clotting requires the demonstration of intravascular fibrin deposits, yet only three of 31 patients with acute promyelocytic leukemia and hypofibrinogenemia studied post mortem had intravascular thrombi,^{2,16,24} and in the present case none was found after careful search. Absence of thrombi is not unusual in well documented instances of intravascular clotting associated with various diseases.¹⁷ The probable explanation is a release of activator from the vascular endothelium directly into the thrombi, causing local activation of plasminogen and antemortem lysis without significant activation of circulating plasminogen. However, if the entire reduction in fibrinogen found in our case were due either to primary or secondary fibrinolysis, one might have expected to find a higher titer of circulating fibrinolytic degradation products in the serum. It is possible, therefore, that mechanisms other than disseminated intravascular coagulation or primary fibrinolysis are responsible for the coagulation defect in this disorder.

Terminally, lysozymuria occurred in the case here reported. This finding, which occurs in monocytic and monomyelocytic leukemia, is a consequence of accompanying lysozymemia.²⁵ Lysozymemia results from dissolution of lysosomes

within the leukemic cells, releasing the enzymatic contents into the blood. Osserman and Lawlor²⁵ observed in the serum of leukemia patients elevation of lysozyme (muramidase) only and no detectable activity of cathepsin or other hydrolases contained in normal leukocyte lysosomes. This apparently selective synthesis of a single enzymatic protein by neoplastic leukocytes is compatible with similar findings in solid tumors. Whether there is any relationship between lysozymemia and the coagulation defects observed in promyelocytic leukemia has not been determined.

What causes the intravascular coagulation in acute promyelocytic leukemia remains to be determined. The recent studies of Quigley²⁶ on extracts of leukocytes in patients with acute promyelocytic leukemia indicate the presence of a substance capable of activating the extrinsic, but not the intrinsic, clotting mechanism. Further fractionation of these abnormal leukocytes and correlation of this apparent thromboplastic activity with the presence of the atypical promyelocytic granules may contribute to our understanding of the pathogenesis and management of the bleeding diathesis which is the clinical hallmark of acute promyelocytic leukemia.

Summary

In a case of acute promyelocytic leukemia and hypofibrinogenemia, the findings of fibrinolysis degradation products in the serum, a prolonged thrombin time and a decreased concentration of Factors V and VIII in the plasma was consistent with a diagnosis either of disseminated intravascular coagulation or primary fibrinolysis. Decreased concentration of Factor X suggested disseminated intravascular clotting, as this factor is not destroyed by plasmin. An apparent increase in Factor IX activity did not suggest lysis and may have been, in reality, a reflection of the presence of circulating activated Factor X resulting from disseminated intravascular clotting. Thrombocytopenia most likely resulted from lack of megakaryocytes in the marrow; it could also have been caused by disseminated intravascular clotting but not primary fibrinolysis.

Only three to thirty-one reported patients with acute promyelocytic leukemia and hypofibrinogenemia studied post mortem had intravascular thrombi and none was found in the present case. If this is to be explained by pre mortem fibrinolysis, a higher titer of fibrinolysis degradation products might have been expected.

Although disseminated intravascular coagulation is the most likely cause of the coagulation abnormalities in this syndrome, further documentation is required.

GENERIC AND TRADE NAMES OF DRUGS

6-mercaptopurine (6-MP)—Purinethol®

Vincristine sulfate—Oncovin®

REFERENCES

1. Croizat, P., and Favre-Gilly, J.: Les Aspects du Syndrome Hémorragique des Leucémies, *Sangre*, 20:417-421, 1949.
2. Baker, W. G., Bang, N.U., Nachman, R. L., Raafat, F., and Horowitz, H. I.: Hypofibrinogenemic hemorrhage in acute myelogenous leukemia treated with heparin—with autopsy findings of massive intravascular coagulation, *Ann. Intern. Med.*, 61:116-123, July 1964.
3. Ben-Zeev, D., Schwartz, S. O., and Friedman, I. A.: Promyelocytic-myelocytic leukemia as a terminal manifestation of chronic granulocytic leukemia, *Blood* 27:863-870, June 1966.
4. Ratnoff, O. D., and Menzie, C.: A new method for the determination of fibrinogen in small samples of plasma, *J. Lab. Clin. Med.*, 37:316-320, Feb. 1951.
5. Owren, P. A., and Aas, K.: The control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin, *Scand. J. Clin. Lab. Invest.*, 3:201-208, 1951.
6. Borchgrevink, C. F., Pool, J. G., and Stormorken, H.: A new assay for factor V (Proaccelerin-accelerin) using Russell's viper venom, *J. Lab. Clin. Med.*, 55:625-632, April 1960.
7. Pool, J. G., and Robinson, J.: Assay of plasma antihemophilic globulin (AHG), *Brit. J. Hemat.*, 5:17-23, Jan. 1959.
8. Kropatkin, M. L., Hoag, M. S., and Aggeler, P. M.: Estimation of factor IX (PTC) activity of human plasma. In *Blood Coagulation, Hemorrhage and Thrombosis. Methods of Study*, L. M. Tocantins, and L. A. Kazal, (eds.): Grune and Stratton, Inc., New York, 1964, p. 125.
9. Bachmann, F., Duckert, F., and Koller, F.: The Stuart-Prower factor assay and its clinical significance, *Thromb. Diath. Haemorrh.*, 2:24-38, Aug. 1958.
10. Astrup, T., and Müllertz, S.: The fibrin plate method for estimating fibrinolytic activity, *Arch. Biochem.*, 40:346-351, Oct. 1952.
11. Alkjaersig, N., Fletcher, A. P., and Sherry, S.: E-aminocaproic acid: An inhibitor of plasminogen activation, *J. Biol. Chem.*, 234:832-837, April 1959.
12. Merskey, C., Kleiner, G. J., and Johnson, A. J.: Quantitative estimation of split products of fibrin in human serum, relation to diagnosis and treatment, *Blood*, 28:1-18, July 1966.
13. Didisheim, P., Trombold, J. S., Vandervoort, R. L. E., and Mibashan, R. S.: Acute promyelocytic leukemia with fibrinogen and factor V deficiencies, *Blood*, 23:717-728, June 1964.
14. Rosenthal, R.: Acute promyelocytic leukemia associated with hypofibrinogenemia, *Blood*, 21:495-508, April 1963.
15. Hillestad, L. K.: Acute promyelocytic leukemia, *Acta. Med. Scand.*, 159:189-194, Nov. 1957.
16. Parker, M. G., and Lowney, J. F.: Acute promyelocytic leukemia, *Missouri med.*, 62:374-378, May 1965.
17. Merskey, C., Johnson, A. J., Kleiner, G. J., and Wohl, H.: The defibrination syndrome: Clinical features and laboratory diagnosis, *Brit. J. Haemat.*, 13:528-549, July 1967.
18. Bernard, J., Lasneret, J., Chrome, J., Levy, J. P., and Boiron, M.: A cytological and histological study of acute promyelocytic leukemia, *J. Clin. Path.*, 16:319-324, July 1963.
19. Fletcher, A. P., Alkjaersig, N., and Sherry, S.: Pathogenesis of the coagulation defect developing during pathological plasma proteolytic ("fibrinolytic") states. I. The significance of fibrinogen proteolysis and circulating fibrinogen breakdown products, *J. Clin. Invest.*, 41:896-916, April 1962.
20. Alkjaersig, N., Fletcher, A. P., and Sherry, S.: Pathogenesis of the coagulation defect developing during pathological plasma proteolytic ("fibrinolytic") states. II. The significance, mechanism and consequences of defective fibrin polymerization, *J. Clin. Invest.*, 41:917-934, April 1962.
21. Nussenzweig, V., Seligmann, M., Pelmont, J., and Grabar, P.: Les Produits Dégénération du Fibrinogène Humain par la Plasmine. I. Séparation et Propriétés physicochimiques, *Ann. Inst. Pasteur.*, 100:377-389, 1961.
22. Nussenzweig, V., Seligmann, M., and Grabar, P.: Les Produits de Dégénération du Fibrinogène Humain par la Plasmine. II. Etude Immunologique: Mise en Evidencé D'Anticorps Anti-fibrinogène Natif Possédant des Spécificités Différentes, *Ann. Inst. Pasteur.*, 100:490-508, 1961.
23. Nussenzweig, V., and Seligmann, M.: Analyse par des Méthodes Immunochimiques de la Dégénération par la Plasmine du Fibrinogène Humain et de la Fibrine à Différents Stades, *Rev. Hémat.*, 15:451-466, 1960.
24. Pittman, G. R., Senhauser, D. A., and Lowney, J. F.: Acute promyelocytic leukemia: A report of 3 autopsied cases, *Amer. J. Clin. Path.*, 46:214-220, Aug. 1966.
25. Osserman, E. F., and Lawlor, D. P.: Serum and urinary lysozyme (Muramidase) in monocytic and monomyelocytic leukemia, *J. Exp. Med.*, 124:921-951, Nov. 1966.
26. Quigley, H. J.: Peripheral leukocyte thromboplastin in promyelocytic leukemia, *Fed. Proc.*, 26:648, Mar.-Apr. 1967.

MEDICAL STAFF CONFERENCE

Multiple Myeloma and Pneumonia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The case summary will be given by Julian Zener.

DR. ZENER:† This is the third U.C. Medical Center admission for this 58-year-old Caucasian housewife, who was admitted 15 October with the chief complaint of fever and headache. The patient had good health until 17 months before admission, when she began to have pain in the right anterior chest and below the scapula. X-ray films showed a mass adjacent to the right fifth rib. Subsequently the rib was partially resected and the histologic findings were consistent with plasmacytoma. The patient's hematocrit was noted to have fallen from 42 to 25 percent during the preceding six months. She received multiple blood transfusions, and administration of melphalan (Alkeran®) was begun, 2 mg daily at first, then 6 mg daily. Anemia recurred, leukopenia developed and she was admitted to the U.C. Medical Center for the first time, 13 months before the present admission, because of marrow depression. Laboratory data on that admission included a hematocrit of 16 percent, leukocytes 800 per cu mm and platelets 177,000 per cu mm. Total serum protein was 12.7 gm per ml, with a homogeneous spike of 7.6 gm between the beta and gamma regions. Examination of sternal marrow aspirate confirmed the diagnosis of multiple myeloma. The patient was treated with reverse isolation and multiple blood

transfusions. Febrile transfusion reactions occurred on two occasions. Subsequent transfusions using blood poor in white cells were reaction free.

Following discharge from the hospital, the patient's transfusion requirement remained high. Eleven months before the present admission she was readmitted for intercurrent upper respiratory infection with fever. Bence Jones protein was detected. Chest films and cultures were unremarkable and the patient responded promptly to intravenous hydration and penicillin.

During the past 11 months, the patient has been followed closely in the hematology clinic here and has been on a regimen of prednisone 80 mg every other day, low doses of melphalan and intermittent parenteral androgens. Transfusion requirements have fallen to zero. A radio-iron marrow scan four months before admission demonstrated peripherally active marrow. Despite migratory bone pain the patient has remained moderately active. She does some of her housework still, and prepares most of the meals for her family.

The present admission was prompted by a week of fever associated with a right middle lobe infiltrate as observed on an x-ray film. Family history is remarkable in that the patient's father and a sister died of Hodgkin's disease.

At the time of admission the patient had herpetic eruptions on her upper lip. Blood pressure 130/78 mm of mercury, the pulse rate was 100 and regular, respirations 24, temperature 38°C, (100.4°F).

*Lloyd H. Smith, Jr., M.D.: Professor and Chairman, Department of Medicine.

†Julian Zener, M.D.: Resident in Medicine.

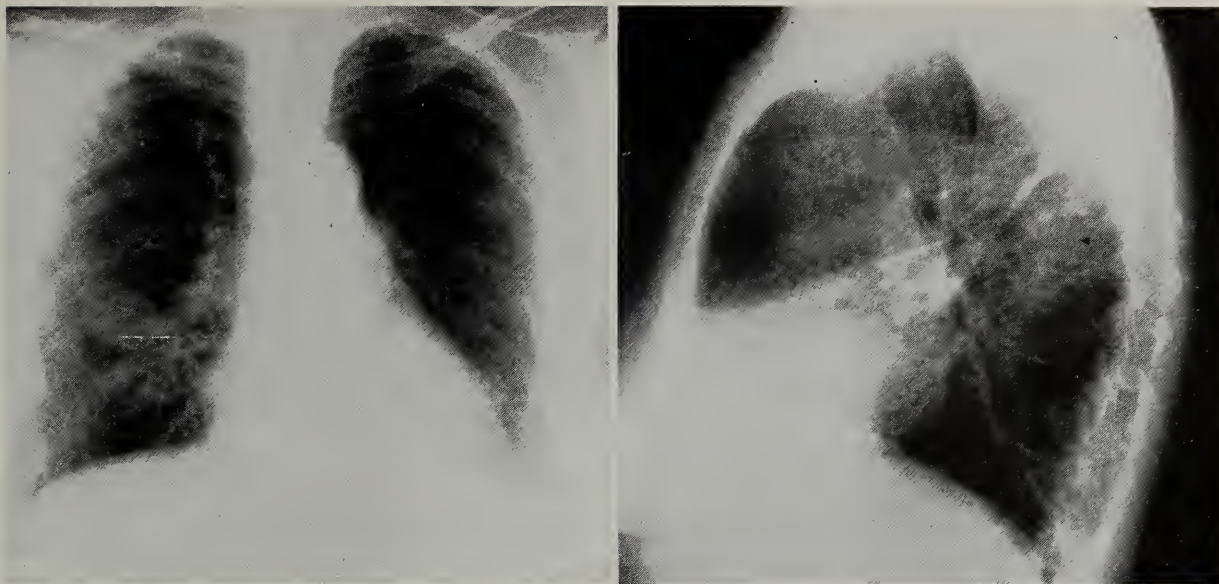


Figure 1.—Films of chest demonstrate bilateral broncho-pneumonia with the most extensive changes in the right middle lobe. Film at right shows some loss of volume of the right middle lobe as manifested by depression of the minor fissure. There is collapse of several of the thoracic vertebrae.

Coarse breath sounds were heard over the lower right chest. A grade II/VI holosystolic apical murmur was present and the spleen was palpable 2 cm below the left costal margin.

Laboratory data included hematocrit of 26 percent, leukocytes 4,200 per cu mm, with 84 percent polymorphonuclear cells. On urinalysis, 2+ proteinuria was noted. Serum electrolytes were within normal limits. Serum albumin was 3.2 gm, serum calcium 8.4 and serum phosphorus 2.2 mg per 100 ml. Creatinine clearance was 95 ml in one minute. Serum protein was 13.2 gm per 100 ml with a 7.6 gm homogeneous gamma spike. Marrow biopsy revealed that plasma cells made up 80 to 90 percent of the marrow cells. A culture of tracheal aspirate grew *Hemophilus influenzae* and the patient was treated with intravenous hydration, intermittent positive pressure breathing, and sodium cephalothin. Defervescence occurred within three days. The tentative diagnosis was multiple myeloma complicated by anemia, bone pain and infection.

DR. SMITH: Thank you very much. I think we should see the x-ray films now.

DR. JAMES E. YOKER:* A film of the chest taken in 1966 demonstrates resection of the right fifth rib (Figure 1). There is considerable scarring and reaction secondary to that operation. The cardiac silhouette is at the upper limits of normal in

size, perhaps related to anemia. The lung fields, otherwise, are clear. A lateral film of the chest (Figure 1) taken at the same time shows that the vertebral bodies are intact although demineralized. Generalized demineralization may be the first indication of multiple myeloma. A film taken two weeks ago shows considerable changes. Bilateral patchy infiltrates are present in both lung fields, suggesting bronchopneumonia. The most extensive changes are in the right mid-lung fields. Lateral films of the chest demonstrate collapse of at least two of the mid-thoracic vertebral bodies as well as confluent pneumonia in the right middle lobe. Films taken yesterday show that the diffuse bronchopneumonia has largely cleared. An area of atelectasis remains on the left side, however. The rib cage is not adequately visualized to rule out pathological fractures. Lumbar spine films also demonstrate lytic areas consistent with multiple myeloma. These changes are best shown in the third lumbar vertebral body where there is a loss of continuity of the anterior margin of the vertebral body and partial collapse (Figure 2).

DR. SMITH: Thank you very much. We are fortunate to have Dr. George Brecher with us this morning. I think Dr. Brecher is going to demonstrate the marrow findings in this patient.

DR. BRECHER:* Thank you, Dr. Smith. I am glad to have the opportunity not only to show you

*James E. Yoker, M.D.: Assistant Professor of Radiology.

*George Brecher, M.D., Professor of Clinical Pathology.

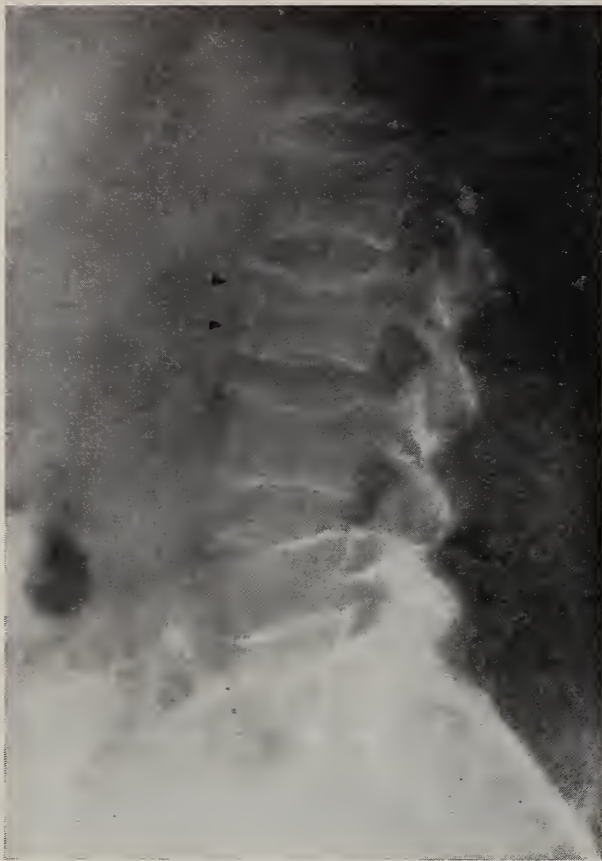


Figure 2.—A lateral film of the lumbar spine shows partial collapse and loss of continuity of the anterior margin of the third lumbar vertebral body due to multiple myeloma.

the bone marrow but also to comment on the dry taps which we obtained in this patient initially. A dry tap is hardly ever due to the incompetence of the operator. It is only very rarely due to reduction of the bone marrow elements, although this is the explanation commonly given. In my experience a dry tap usually indicates an underlying serious disease process which happens to increase reticulum fibers, which then hold the bone marrow elements together a little more firmly than normal and prevent the breaking up of bone marrow into individual particles during aspiration that is prerequisite to obtaining an adequate specimen.¹ In such circumstances a second attempt usually is futile also because the underlying disease process and the reticulum fibrosis persist. The remedy is to obtain a bone marrow specimen by use of a modified Vim-Silverman needle known as the Westerman-Jensen needle.* The specimen so obtained is quite large, yet needle biopsy is no more painful to the patient than aspiration, and it can

*Becton-Dickinson Co., Rutherford, N. J. Cat. #01-0004-WJ- (10x4-1/4).

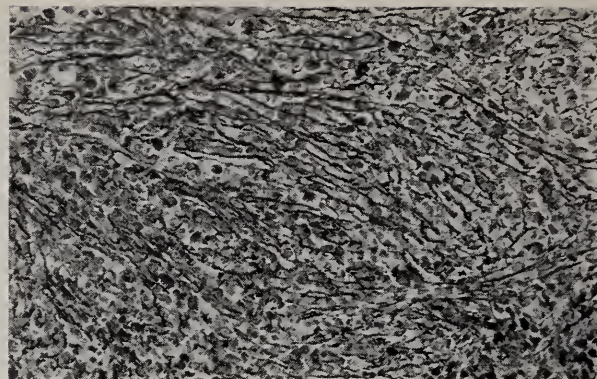


Figure 3.—Reticulum fibrosis of marrow. Silver reticulum stain, 250 X.

be done as an office procedure. The more formidable open biopsy should now be abandoned. It provides much bone but often little marrow while the relatively painless needle biopsy specimen usually contains mostly marrow.²

The needle biopsy specimen in the present case contained decidedly hypercellular marrow with only a few fat cells and the expected increase in reticulum fibers (Figure 3). Several areas consisted largely of normal elements with islands of normoblasts, megakaryocytes and segmented neutrophils. In other areas the marrow was replaced by a uniform cell type which resembled plasma cells (Figure 4). The touch preparation was inadequate but in a few areas permitted recognition of most of the infiltrating cells as plasma cells, while a few resembled small lymphocytes (Figure 5). The marrow may thus be categorized as consistent with plasmocytic malignant disease and the diagnosis is myeloma. However, it must be noted that occasionally apparently typical plasma cells produce macroglobulins rather than myeloma pro-

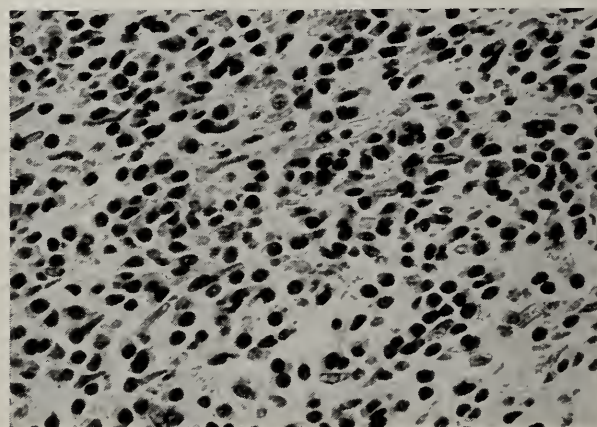


Figure 4.—Replacement of marrow by tumor. Note predominant cell type, resembling plasma cells. H & E stain, 250 X.

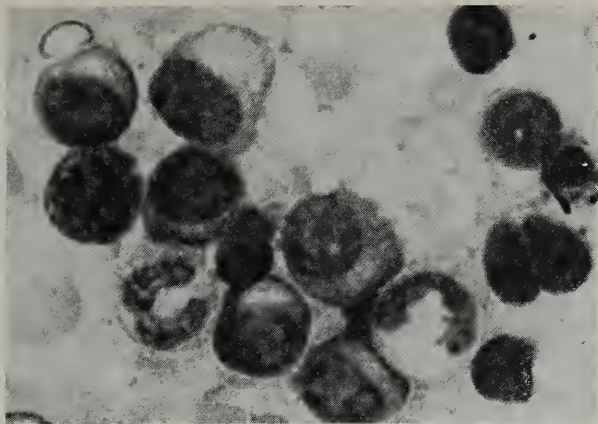


Figure 5. — Infiltrating tumor cells predominantly plasma cells at left and lymphocytes at right. Two stab cells and a normoblast (on bottom) represent admixture of cells from areas of normal marrow. Touch preparation of marrow plug, 1000 X.

teins, while even more rarely a malignant process with lymphocytes as the predominant cell type produces a gamma myeloma protein.

DR. SMITH: Thank you very much, Dr. Brecher. There are many aspects of this patient's illness which could be selected for presentation this morning at Medical Grand Rounds. The diagnosis does not seem to be in doubt on several grounds—the clinical presentation, the marrow cytology, and the protein abnormalities. We have elected to concentrate on the presenting complaint, that of infection with pneumonia, and to ask the following question: How does her disease predispose to infection? The disordered synthesis of gamma globulins and the treatment which she has received, which of course included glucocorticoids and substances which have suppressed her marrow, may have contributed to this. We have asked Dr. Sydney Salmon to introduce this topic and to tell us whether or not patients with multiple myeloma have increased susceptibility to infection. If so, why does it occur?

DR. SALMON:* The problem of infection in myeloma is one that is constantly with the physician who sees such patients. It represents the major cause of mortality and one of the significant causes of morbidity in these patients. To give some background, we can point to a survey made shortly before the current era of chemotherapy for multiple myeloma.³ Bacterial infection was found to be considerably more common in patients with multiple myeloma than in patients with a similar allied

disorder, macroglobulinemia. In fact, the incidence of infection in macroglobulinemia is not any higher than in the general hospital population. Patients with myeloma, in contradistinction, were found to have an average of more than two infections per year, which raises questions about which immunological abnormalities present in myeloma would predispose to infection. Serum protein electrophoresis in the majority of patients with myeloma demonstrates a homogeneous discrete increase ("M component" or "spike") in the beta or gamma region. These paraproteins have been isolated and purified and have provided a considerable amount of basic understanding of the protein structure and genetics of the immune globulin system. There are three major immunoglobulins: gamma G, gamma A, and gamma M. Gamma M, or macroglobulin, is not involved in multiple myeloma. The syndrome associated with macroglobulinemia is different in many respects, albeit there are a few similarities. There is a lesser immune globulin, gamma D, which is present in low concentrations in normal human serum, and gamma D spikes have been found in a small number of cases of characteristic multiple myeloma. In addition, there is now another trace immunoglobulin, gamma E, which also has proved to be a very rare myeloma protein type.

Structurally, the gamma globulin molecule has four chains, two of which are heavy, two light. There are two types of light chains, one called kappa and the other called lambda. The heavy chain has been given the designation gamma for gamma G, alpha for A and delta for gamma D. With rare exception any one patient with multiple myeloma will have only one of these immune globulin types present in decidedly increased amount and is therefore said to have a "monoclonal gammopathy." As far as is known, the myeloma protein has no protective antibody function, and appears to be a molecular prototype rather than a specific antibody resulting from immunization. In some patients, only the light chain is synthesized and they have urinary Bence Jones proteinuria as a consequence (Table 1). Many patients will have increased synthesis of both intact immunoglobulin molecules, as well as increased free light chain synthesis.

The immunologic deficiencies which these patients have can be determined in several ways. If one gives a patient with myeloma a series of antigens and measures the antibody responses, com-

*Sydney E. Salmon, M.D., Assistant Professor of Medicine.

TABLE 1.—*The Paraproteins of Plasma Cell Myeloma*

<i>Intact Immunoglobulins</i>	
<i>Immunoglobulin Class</i>	<i>Light Chain Antigen</i>
IgG	Kappa
IgG	Lambda
IgA	Kappa
IgA	Lambda
IgD	Kappa
IgD	Lambda
IgD	Lambda
<i>Free Light Chains</i>	
Kappa (Bence Jones Protein)	
Lambda (Bence Jones Protein)	

pared to a normal population, most of the controls have good antibody responses whereas the myeloma patients often don't respond at all or at best have only low titers of specific antibodies.

In many patients the content of the residual normal immune globulins is reduced to hypogammaglobulinemic levels. Studies of the catabolism of intravenously injected radio-iodinated immune globulins in myeloma patients have in general shown the half life in gamma-G myeloma patients to be shorter than normal. The normal half life for gamma-G globulin is 18 to 20 days, whereas in a patient with gamma-G myeloma it is reduced to somewhere between six and nine days.^{4,5} In contradistinction, patients with agammaglobulinemia often have considerable prolongation of the gamma globulin half life, to perhaps a month or more. The synthetic rate of normal immunoglobulins is often decidedly reduced in patients with myeloma.

In addition to the serum protein abnormalities, there is also evidence for cellular immunologic deficiencies in myeloma. Normal neutrophils or neutrophilic granulocytes from patients with myeloma have been studied with a quantitative system for phagocytosis of yeast particles and have demonstrated impaired phagocytic function when the cells were placed in the presence of high concentrations of gamma globulin. This observation may have pertinence to the fact that the organisms of infection in patients with myeloma are usually Gram-positive and require phagocytosis for resolution.

We have discussed the proteins and the granulocyte, and we might now mention the lymphocyte. Dr. Brecher has shown us that there are morphological overlaps between plasma cells and lymphocytes in the malignant dysproteinemias. One type of study of the lymphocyte which is of interest is lymphocyte culture. Heparinized venous blood is obtained from normals or from subjects with

TABLE 2.—*Abnormalities of Immunity in Multiple Myeloma*

- (1) Increased susceptibility to bacterial infection.
- (2) Synthesis of monoclonal myeloma paraproteins by neoplastic cells.
- (3) Reduced levels of normal immunoglobulins.
- (4) Reduced levels of specific protective antibodies.
- (5) Reduced synthesis rates of normal immunoglobulins.
- (6) Increased catabolic rates of paraproteins and normal immunoglobulins.
- (7) Impaired serum antibody response to antigenic stimulation.
- (8) Granulocytopenia.
- (9) Impaired phagocytosis in the presence of myeloma protein.
- (10) Impaired peripheral lymphocyte function.
- (11) Normal delayed hypersensitivity and homograft rejection reactions.

various disorders. The red cells are sedimented from the blood and the supernatant leukocytes are removed, washed and then cultured in tissue culture medium to which plant mitogens such as phytohemagglutinin (PHA) or specific antigens to which the patient had been previously immunized, can be added.

If no additives are placed in the cultures after three days the lymphocytes still appear to be small, and morphologically quite similar to those which were placed in culture initially. In addition to morphologic studies, with the addition of a labeled DNA or RNA precursor either thymidine or uridine, cellular synthesis of nucleic acids can also be measured. Very strikingly if one adds PHA, lymphocytes undergo a pronounced change in morphologic appearance. They become larger and are transformed in large part to look like primitive blast cells, although some of the cells do look somewhat like plasma cells. Radioactivity determinations on PHA-stimulated cells demonstrates a decided increase of cellular incorporation of precursors into DNA and RNA. In patients with multiple myeloma, there is a defect in peripheral lymphocyte function demonstrated as a reduction of PHA-stimulated DNA and RNA synthesis compared with that observed in normal controls.⁶ The defect is present whether or not the patient is receiving chemotherapy. This finding is of considerable interest because the peripheral lymphocyte population is sampled rather than the abnormal bone marrow plasma cells. In the above test, lymphocytes from macroglobulinemic subjects have responded in a manner similar to the response of lymphocytes from myeloma patients, whereas patients with other forms of hyperglobulinemia

such as connective tissue disorders and chronic infection have not had a lymphocyte defect of this character. Although the myeloma lymphocyte is defective *in vitro*, the patients have normal delayed hypersensitivity and homograft rejection reactions.^{7,8}

The immunologic abnormalities in myeloma (Table 2) include synthesis of gamma-G, gamma-A, gamma-D or Bence Jones paraproteins without known protective antibody function, decreased levels of normal immunoglobulins and specific antibodies, as well as decreased rates of normal immunoglobulin synthesis and increased rates of catabolism. There is impaired response to antigenic stimulation with the reduced levels of serum antibody probably reflecting the net result of decreased synthesis as well as increased catabolism of specific antibodies. Granulocytopenia is a common finding. Phagocytic function by granulocytes also appears to be impaired in the presence of high concentrations of myeloma globulin, and there is a defect of lymphocyte nucleic acid metabolism.

This background information suggests that patients with myeloma have an immunologic deficiency syndrome which is somewhat similar to that seen in patients with agammaglobulinemia. The analogy is not complete, however, inasmuch as catabolic rates of immune globulins are increased in myeloma and usually decreased in agammaglobulinemia. Because of the functional hypogammaglobulinemia which occurs in myeloma, it was of interest to study the patients with myeloma to see whether their susceptibility to infection could be reduced by the administration of normal gamma globulin. This was done in cooperation with five institutions in the eastern United States in a double blind clinical study involving about fifty patients with plasma cell myeloma.⁹ The patients received 20 ml of gamma globulin or a matched albumin placebo intramuscularly every two weeks for up to 19 months and tolerated this treatment extremely well.

A total of 26 major infections occurred, of which 20 were pneumonia or acute purulent bronchitis. The major offending organism was pneumococcus. There were a smaller number of cases of acute pyelonephritis and a few miscellaneous infections. Gamma globulin did not protect against infection in these patients. There were seven patients infected in the gamma globulin group, and eight in the control group. In fact, two of the patients in the gamma globulin group had mul-

tipl infections—pneumonia five times in one case and four times in the other; and both of the patients had recurrent pneumococcal pneumonia despite gamma globulin therapy.

The obvious question, then, comes to why gamma globulin therapy did not protect against infection in myeloma. Several factors that were mentioned previously are pertinent, including the increased catabolic rate of the gamma globulin and perhaps the impairment of neutrophil function in myeloma. Multiple pathologic rib fractures with resulting splinting or atelectasis may set the stage for infection. As to the effects of chemotherapy or steroid therapy, it would appear that the overall incidence of infection may actually be reduced now in the era of appropriate chemotherapy. The induction of significant remissions may be reducing susceptibility to infection. Most of the patients responded quite appropriately to bactericidal antibiotics administered at the time infection was diagnosed. It is currently my practice to start giving antibiotics to patients with myeloma whenever a deep cough with sputum production develops. The majority of patients in this study with major infections were not in a state of disease remission when the infections developed. The patient presented today had progressive disease. Although her hematocrit had been corrected as a result of androgen and steroid therapy, the levels of serum myeloma protein persisted and lytic bone disease progressed.

We have discussed only a few aspects of multiple myeloma and there are a number of other problems which these patients face. Much remains to be learned about the natural history of this disease. There may be genetic predispositions or environmental factors which predispose to the development of myeloma. It is interesting that the patient we discussed had two first order relatives with lymphoproliferative disorders. It is quite possible that the lymphocytes of such patients are subject to a common genetic defect which predisposes to development of a lymphatic neoplasm. Although the plasma cell is probably derived from the lymphocyte at some stage in its development, the plasma cell in myeloma is quite different from the normal in that a self-sustaining line of neoplastic plasma cells develops which has the capacity to produce large amounts of a monotonously homogeneous monoclonal immunoglobulin. The associated immunological deficiency syndrome may be related to a proliferative defect in the re-

maining "untransformed" lymphocytes.

The pathophysiologic features of this lymphoid neoplasm are beginning to form a coherent pattern, which may lead to an explanation of many of the diverse manifestations of multiple myeloma.

DR. SMITH: Thank you very much, Dr. Salmon. Dr. Fudenberg, would you like to make some comments about this problem?

DR. HUGH FUDENBERG*: I would like to ask several questions:

- What is the difference between the frequency of infections in patients with high paraprotein peaks and those with low levels of myeloma protein?

- Were the patients with infections distinguished by having very low serum albumin levels? As you know, hypoalbuminemia occurs in myeloma. *In vitro* some of the effects produced by myeloma proteins can be corrected, at least in part, by albumin.

- How much albumin was given to the patients receiving albumin controls? Was it sufficient to raise their levels of serum albumin?

- Could the failure to distinguish between the gamma globulin-treated group and the albumin-treated group be due to the fact that the patients receiving albumin had their serum levels raised and their defenses thereby improved?

DR. SALMON: With regard to the first question, there was no difference in frequency of infection between patients with high paraprotein levels and those with small peaks. The patients with the highest paraprotein levels tended to have lower serum albumin levels. The dose of 1 gm of albumin that was administered was not sufficient to alter the serum albumin concentration. There was no obvious relationship between serum albumin or myeloma protein levels and frequency of infection.

There are other questions one could raise about using a control which conceivably could increase the ability for the reticuloendothelial system to phagocytize and hence improve host resistance. In any case there were no differences between the two groups, and I feel that the control that was used was adequate and did not obscure the experimental observations.

DR. WALLACE EPSTEIN†: Would the exposure of normal lymphocytes to the myeloma protein in-

duce the same lack of response to PHA mitogen stimulation?

DR. SALMON: It will not. In the type of experiment that you describe we have studied plasma of untreated patients whose lymphocytes were defective. Normal lymphocytes function normally in the presence of myeloma plasma. Thus, the myeloma lymphocyte defect appears to be cellular.

DR. MALCOLM MACKENZIE*: Secretory gamma-A globulin appears to be important in the defense against infections. In view of the fact that most of these infections are pulmonary, are there any data available to state whether the secretory immune globulins in the saliva or bronchial secretions of myeloma patients contain gamma-A globulins?

DR. SALMON: That is an excellent question and deserves careful investigation. Normal serum gamma-A globulin levels are frequently reduced in myeloma, and this could possibly pertain also to the secretory gamma-A globulins.

DR. ERNEST JAWETZ†: With reference to the lymphocytes, do you think that the possibility exists that the sampling of cells from lymph nodes would give different results from those obtained from the peripheral blood lymphocyte?

DR. SALMON: We have not done studies such as this. It was intriguing that there was a defect in the peripheral lymphocyte as measured with the system. The response to the phytohemagglutinin may not be directly related to *in vivo* lymphocyte responses in patients, or responses to specific antigens, but this has not been looked at. It would be worth studying. Methodologically, these latter problems are somewhat more difficult. The peripheral lymphocyte population in itself is quite heterogeneous, and there are probably many different "kinds" of circulating lymphocytes which look morphologically similar.

DR. SMITH: Is it actually true that myeloma protein has been shown not to have antibody function? It was my impression that one or two cases existed in which antibody function had been demonstrated despite the monoclonal nature of the protein.

DR. SALMON: Yes, Dr. Smith, it is true that there are one or two cases now in which antibody activity has been demonstrated. The most convincing

*H. Hugh Fudenberg, M.D., Professor of Medicine.

†Wallace Epstein, M.D., Associate Professor of Medicine.

*Malcolm MacKenzie, M.D., Assistant Professor of Medicine.

†Ernest Jawetz, M.D., Professor of Pathology.

demonstration was reported very recently and showed a myeloma protein that had very specific binding capacity for a synthetic substance, the dinitrophenyl hapten. This specific antibody function was detected in one protein of a large number of myeloma proteins which were screened for this hapten specificity. A few macroglobulins from patients with Waldenström's macroglobulinemia have antibody activity against normal gamma globulin and are currently under investigation in several laboratories. It may well be that every myeloma protein has a different specific antibody function. We may just not know what the antigen is with which to recognize it.

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REFERENCES

1. Kundel, D. W., Brecher, G., Bodey, G. P., and Brittin, G. M.: Reticulin fibrosis and bone marrow infarction in acute leukemia, *Blood*, 23:526, 1964.
2. McFarland, C. N., and Dameshek, W.: Biopsy of bone marrow with Vim-Silverman needle, *JAMA*, 166:1464, 1958.
3. Fahey, J. L., Scoggins, R., Utz, J. P., and Szwed, C. F.: Infection antibody response and gamma globulin components in multiple myeloma and macroglobulinemia, *Amer. J. Med.*, 35:698, 1963.
4. Lippincott, S. W., Korman, S., Fong, C., Stuckley, E., Wolins, W., and Hughes, W. Z.: Turnover of labeled normal gamma globulin in multiple myeloma, *J. Clin. Invest.*, 39:565, 1960.
5. Solomon, A., Waldman, T. A., and Fahey, J. L.: Metabolism of normal 6.6 S gamma globulin in normal subjects and patients with macroglobulinemia and multiple myeloma, *J. Lab. & Clin. Med.*, 62:1, 1963.
6. Salmon, S. E., and Fudenberg, H. H.: Defective lymphocyte nucleic acid metabolism in multiple myeloma and macroglobulinemia, Submitted to *Blood*, accepted for publication, July, 1968. Abstract: *Clin. Research*, 16:124, 1968.
7. Linton, A. L., Dunnigan, M. G., and Thomson, J. A.: Immune responses in myeloma, *Brit. Med. J.*, II:86, 1963.
8. Salmon, S. E.: Unpublished observations.
9. Salmon, S. E., Samal, B. A., Hayes, D. M., Hosly, H., Miller, S. P., and Schilling, A.: The role of gamma globulin for immunoprophylaxis in multiple myeloma, *New Eng. J. Med.*, 277:1336-1340, 1967.

Mission Neighborhood Health Center, San Francisco

GEORGE K. HERZOG, JR., M.D., *San Francisco*

IN LATE 1966 the San Francisco Medical Society learned that a neighborhood health center was being considered for one of the city's "poverty pockets." Under the 1966 amendment to the Economic Opportunity Act of 1964, the Office of Economic Opportunity (OEO) was authorized to consider for funding, proposals that would provide assistance for development and implementation of comprehensive health center services for the poor. In other areas of the United States these centers had as their delegate agency either a medical school, a public health department or a major teaching hospital (Columbia Point project—Tufts Medical School; Denver project—Denver Department of Public Health; Lower East Side Manhattan project—Beth Israel Hospital; Watts project—USC School of Medicine; Morrisania Health District, The Bronx project—Montefiore Hospital; Miles Square, Chicago, project—Presbyterian St. Luke's Hospital; North Lawndale, Chicago project—Mount Sinai Hospital).

In some of these communities there was open controversy between the local medical societies and the delegate agencies. Medical society interest was too late and too little. To avoid these problems, the San Francisco Medical Society's board of directors authorized exploratory meetings with the local Economic Opportunity Council (EOC), the San Francisco Dental Society, the San Francisco Public Health Department and the University of California School of Medicine.

From many discussions there evolved a delegate agency known as CHAP (Citizens Health Affairs Program). The CHAP board has five directors appointed by the San Francisco Medical Society, four by the San Francisco Public Health Department (of whom three are also members of the society), a San Francisco Dental Society repre-

sentative, and five appointed by the neighborhood EOC board from among citizens of the area.

Problems lie in three general areas: (1) working along with government "bureaucracy"; (2) keeping the doctors practicing in the area happy and not feeling the center will ruin their practices; (3) convincing the people of the area that the center belongs to them, is to help them, and is not another form of dole or an attempt to find people for "experiments."

The OEO representatives have been most cooperative. Many meetings were held, both in Washington and San Francisco, and there were innumerable phone calls. These centers are new, with different problems in each area—but problems that can be solved if each side gives a little. One difficulty was that deadlines constantly were being set. It was sometimes practical to ignore them. Another problem has been change of personnel at the Washington level. I can say, however, that cooperation has always been excellent.

As to keeping doctors happy, meetings were held with all who practiced in the area to be served. They nominated doctors from their group for a Medical Advisory Board, which has also representatives from the University of California Schools of Medicine, and professions of pharmacy, dentistry, and nursing. This board advises the project director on all professional appointments and policies. By law, Medi-Cal and Medicare patients are entitled to come to the center if they fall under the poverty index ceiling, but they are discouraged from doing this.

The area people have five representatives on the CHAP board and, even more important, have a Neighborhood Health Council of 21 members who are appointed by the Mission area EOC chairman from among the people of the area, primarily recipients of care. The council is concerned with policy, center hours, grievances and all non-profes-

The author is chairman of the CHAP board (Citizens' Health Affairs Program, San Francisco).

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sional appointments. All has not been serene, but grievances have been settled and a feeling of trust has developed between the area people and the medical representatives.

The EOC board selected the Mission area of San Francisco as the target area. This area has 120,000 residents, of whom approximately 30,000 will be eligible for the center. They are for the most part Mexican, Central American and South American. About 20 percent are Negroes who live in one area of Potrero Hill. There are many children, many Spanish-speaking immigrants, and a surprisingly large group of American Indians. There are two low-cost housing projects in the area served.

The center is housed in a building at 240 Shotwell Street, which has been rented with the possibility of purchase under FHA financing. Extensive remodeling is now being undertaken, and it is hoped the facility will be open in November of this year. In the meantime, interim facilities have been opened in the parking lot of the building, with four large trailers arranged in box formation, and a central reception area. The trailers are approximately 10 x 50 feet. One has complete dental facilities, another medical facilities, and two are for administration offices and supplies. The trailers are fixed installations, being connected to the city sewerage system and electricity and telephone services. Each has a bathroom and a waiting area.

Hours for the center were decided by the people themselves as represented by the Neighborhood Health Council, and by the CHAP board. All the workers are paid; this is not a volunteer organization and one of the main functions of the center will be to provide jobs for people in the area. Mission area residents are being trained as neighborhood health workers. They will become acquainted with people in the area, encourage them to come to the center and assist them in finding babysitters and obtaining transportation. They are to involve themselves with the families and offer whatever assistance is necessary, not just assistance having to do with medical care.

The doors of the center will always be open, although routine hours are from 8 a.m. to 10 p.m. five days a week, with a half day on Saturday. The center is concentrating on the team concept. Teams will be set up to provide a full range of care, with a primary physician aided by physician specialists to provide pediatric, obstetrical, surgical and other specialty services as needed. A full range of psy-

chiatric services will be available. Included on each team will be a dentist, a public health nurse, a registered nurse, a licensed vocational nurse, a receptionist, a social worker and neighborhood health aides. As far as possible, patients will see the same team at each visit. However, all families will have, as far as practicable, free choice of the team by which they wish to be served. Ten such teams are planned. The primary physician will have responsibility for coordination of effort.

When a patient is entitled to private hospital care by reason of adequate insurance or government funds, any of the major accredited hospitals of San Francisco may be utilized. There is no single back-up hospital. The center physician will arrange hospital care according to his own wishes, the medical problems, the patient's wishes, and bed availability. The physician will also arrange for appropriate consultation either from a physician chosen by the patient or from a panel of physicians on the hospital staff. The patient who does not have hospitalization insurance will be referred according to the availability of facilities in San Francisco General Hospital or in the clinics of the other hospitals that have agreed to take a number of these patients. It will be the responsibility of the center physician to follow the patient while in the hospital and insure continuity of care in all cases.

The San Francisco Medical Society has stressed to the people of the area that the physicians are in this for only one reason, to provide better health care for the people in the area. None of the physician members of the CHAP board or the Medical Advisory Board is salaried.

Many people of the area have excellent ideas, their thoughts are stimulating, they keep us from getting into a rut, and make us explain our position every step of the way. The result has been a far greater understanding by the physicians of the problems of the poor. We believe, too, that the people in the area have obtained a greater understanding of medical problems and problems of the physicians themselves. From a public relations standpoint, I feel this has been helpful to medicine.

Since the original announcement of the center, there have been inquiries from medical societies all over the country. Our society may have been the first to become completely involved in a neighborhood health center, but it is far from being the last. It is a long way to completion of the job, but it has been gratifying to see the gradual development of a functioning neighborhood health center.

The State's Eighth Medical School

University of California, Irvine

A MOST UNUSUAL series of events has converged in California to culminate in the development of a college of medicine that will possess some of the most attractive characteristics that will be available for medical education anywhere. Picture the circumstance of a developing college that has the opportunity to join with a newly developing major campus of one of the most distinguished universities in the world, located at Irvine, one of the garden spots of Southern California at the upper reaches of Newport Beach Harbor, surrounded by a swelling population soon to be the geographic center of a West Coast megalopolis. Nearby lies the 83,000 acre Irvine ranch that is being developed into one of the most carefully planned and beautiful communities in the world. Picture also the resources of a rapidly accumulating university faculty of great distinction and nearby communities reacting with pride and pleasure to the entire event, and you will be witnessing a medical and health facility that is destined to become a major health resource of the West, indeed of the nation.

This happy series of events is occurring in the State of California, where careful students of the health requirements of that vigorous state recognize the great need for new medical schools, and noted even ten years ago in a governor's report that ten new medical schools should be built by 1975. California, which now imports 75 percent of the physicians it needs, has long been deficient in producing its own. For that matter, this deficiency applies to all members of the health team. Many have acknowledged this requirement of our affluent society and have also recognized that it is one that can no longer be provided by the private sector alone. The expenses are so great that it has become imperative that government be involved either directly, such as through states, or indirectly by extensive federal education and research support.

It was small wonder, therefore, that when the legislature became aware of the availability of the California College of Medicine and of a threat to the college's continuity, it quickly assumed that responsibility and took the first step by affiliating it with its statewide university system in 1964. Soon thereafter the University of California also noted the important fact that the college was producing many fine physicians and the board of regents could avoid the cost and time lag of starting a new medical school sometimes ten or fifteen years before the first class graduates. It was apparent it would be to the university's benefit to take advantage of a college of medicine that already existed and was in production. Thus, the regents in 1965 incorporated the college completely as an integral part of the University of California and its fifth medical school.

Choosing the Site

A problem still remained to be resolved, namely, the best location for its new college. The university proceeded with great care and allocated \$25,000 to review the advantages and disadvantages of all possible sites. Matters of amount of space available for future development, population growth and future urban changes, availability of patients and affiliated nearby hospitals, as well as the careful consideration of the values of a relationship to a general university campus, were reviewed. It was particularly stressed that colleges of medicine are major public resources which must be carefully distributed with minimum territorial overlapping so as to be able to take maximal advantage of their location in relation to future public need. Such spacing assumes greater significance as the various federal programs, such as the Regional Medical Programs, develop and tend to have their areas identified with medical schools.

After careful study, including contacting faculty, local practitioners, the Orange County Medical Association officers and public bodies, the board

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of regents decided that the major overriding factor should be the availability of a major campus. Fortunately, a few years earlier the regents had approved the development of a new University of California general campus at Irvine (UCI). Its dynamic chancellor, Daniel G. Aldrich, Jr., recognized the desirability of a medical school at his campus and early expressed an interest in welcoming the college of medicine if that was to be the decision of the regents. So it was. Thus was started in motion a series of medical educational innovations and plans that are just beginning to unfold.

Basic Objectives and Curriculum

With the college of medicine the fortunate recipient of an assignment to the vigorous young UCI campus with its exciting physical master planning under the overall supervision of the renowned architect, William Pereira, it quickly became apparent to our faculty that this was the golden opportunity to reexamine and evaluate the college's basic objectives and curriculum. Such an opportunity, wherein an over-view can be made of where it has been, what it is doing now, and what lies ahead, comes very infrequently in the life of a medical school. It is an occasion for re-checking old procedures, justifying traditional patterns, and honestly taking the opportunity to see if there is a better way or an improved way to carry out its responsibilities.

Members of the new faculty, including some from the new campus at Irvine, met in a series of faculty conferences and committee meetings to review basic philosophies and objectives for the future and discuss a curriculum that would best put them into effect. They recognized that one basic tenet was research, which is the basis for all medical progress, or, for that matter, all scientific progress. Today's successful medical practice procedure was yesterday's acceptable research procedure. Thus there must be a solid base in research and creative activities. A second tenet that the faculty noted was that without practice and without patients there could be no training of physicians. Thus the medical student, to meet the needs of society as a physician, must be properly trained in the modern techniques and methods of medical practice and procedures. It was agreed that practice should be interpreted broadly to include not only the physician serving his individual patient, but also his service to groups of patients, thereby serving society in its broader social medi-

cal need. Finally, the faculty acknowledged, as a basic requirement for the curriculum, that modern practice has long been, in fact, a team effort. The team is composed of the physician and the practitioners of other allied health disciplines. The young physician in training must be able to recognize the existence of the team and understand its characteristics. He must see his important role in providing leadership quality and ability to the team and must understand why he can no longer function effectively alone.

The basic objectives expressed above are not listed in the order of their relative importance, for each is important in a balanced whole. Creative activity and research, the *sine qua non* of scientific progress, are essential to the development of new methods and critical thinking. Together they make possible the development of a distinguished faculty which is the essential ingredient for excellence in academia. Research here is not only to be in the traditional pre-clinical disciplines, but also the clinical ones. The physician professor gains a great deal from the close collaboration with his confreres in the sciences basic to medicine. Contrarywise, the basic scientists on the medical school faculty profit by the physician's knowledge of the health and disease problems. Thus, there should be strong interdependence among various curricula and departments, not only within the college of medicine itself, but also with excellent resources of the general campus. The curriculum must be designed to tap these resources.

Relationship to Community

The college of medicine of the future must modify its traditional image of predominantly looking inward, and begin to look outward into the community and society. Thus it should early establish as a major posture a cordial relationship with physicians in the area and develop affiliations with local hospitals that might be interested and wish to join with the college of medicine in training young physicians. The faculty acknowledged the importance of new patterns in public health attitudes in relating the medical school with the total community resources and its citizens. The Regional Medical and the Comprehensive Medical programs are examples of these new patterns. Thus the college appointed as its coordinator of the Regional Medical Program its associate dean of Continuing Medical Education. Many joint committee membership appointments between these

programs are resulting in an overall coordinated approach to health problems, wherein the college of medicine is a major component in continuing physician education and innovative demonstration projects at many levels of health care.

One of the most challenging topics, and one receiving the greatest detailed consideration, has been the medical curriculum. The move to a new campus was an opportunity for review and an opportunity for change, keeping in mind the axiom of using the most promising of the new and retaining the best of the old. The faculty recognized the many weaknesses in the traditional curriculum, such as unnecessary duplication, a tendency for too much detail, the resistance existing in artificial boundaries between traditional departments, and the like. It noted that the curriculum of the past did not always use the physical plant as efficiently as possible. Particularly important is the fact that medical students do not enter medicine as a stereotype group, except for their carefully selected characteristics of superior native intelligence, unquestioned moral integrity and high motivation to become physicians.

The student often has pursued varied courses with different major emphasis, even including various academic degrees. He frequently knows specifically what he wants in medicine — family practice, specialization, advanced degrees. Any curriculum, therefore, to be fair to the unusual talents of these young people, must not only assure that they all are instructed in the basic "core" of medical facts necessary for all physicians to know, but should permit them an informed choice in selecting special avenues for academic development beyond the "core" knowledge.

After much discussion and many meetings, the following series of characteristics was incorporated into the new curriculum: The enthusiasm of the entering student must be preserved and his motivation enhanced by earlier contact to patients with a carefully graded program of exposure. The "core" of basic knowledge necessary to be a physician is required, with the preclinical "core" occupying the first four quarters, and the clinical "core" the second six quarters. The student is to be given more choice in course selection as upper classmen — this not to mean free time just for "contemplation," but faculty-supervised and academically productive. Finally the faculty considered, as a key component of its curricular objectives, the imbuing of students with the necessity of

remaining lifetime scholars, with the medical degree no more than a milestone. Each student is to be constantly reminded of his obligation to continuing medical education during his active practice and to come to look upon his college of medicine and the hospital where he practices as his logical lifetime postgraduate center. In order to obtain these objectives, the curriculum is to be designed to take full advantage of automation and computer sciences for health education instruction.

Multidisciplined Teaching Concept

To effect the curriculum changes, there will be major organizational and chronological modifications. Instead of the traditional departments in the first two years, there are to be teaching units referred to as curricula. These are multidiscipline instructional units, each of which will assume full responsibility for the students during a full quarter of the year. The traditional Department of Anatomy is now the Curriculum of Human Morphology involving the study of structure at all levels — molecular, micro and macrolar — that is, cytology, anatomy, histology, embryology, and the like. The Curriculum of Environmental Correlates includes such traditional areas as microbiology, preventive medicine, bionomics and community diseases. The other remaining two curricular areas are Human Function and, finally, Introduction to Disease.

These curricula are designed for the efficient use of multidiscipline laboratories and teaching. The laboratories permit maximal efficiency by centralized supervisory administration and efficient use of major teaching equipment. In the multidiscipline teaching concept there is opportunity for the joint appointments not only between the departments of the college of medicine, but also between medicine and other schools and departments of the campus. Such joint appointments will be in biological sciences, physical sciences, social sciences, and others, and will take advantage of the total resources of the campus for the good of medicine and other disciplines on the campus.

The clinical departments will remain much the same as they are in the traditional curriculum. However, an important modification is the extension of the teaching of the preclinical basic science curricular instruction into the third and fourth years. Included in this is an emphasis on physical medicine and rehabilitation which will permit research in musculo-skeletal disease and body mechanics. This area of instruction and emphasis is

to continue through several of the quarters of the third and fourth years.

Student's Choices in Final Year

In the last two years, the "core" instruction needed in the clinical departments will be completed in time to permit student choice at the end. In the last year the student is permitted to make informed selections, with faculty advisor guidance, in those areas that he would like to emphasize to round out his training in the light of his plans for his medical career.

In summary, it has been possible, with many new faculty members and transferring to a new major campus, to bring major innovations to curriculum, to instruction techniques and to organizational design. The opportunity will be afforded any medical student of special ability to shorten his medical education one calendar year. A student may select from among various avenues of study in designing his final years of medical college training. Not only may he probe special medical preferences, including family practice, he may enroll for advanced degrees, if that is his inclination. This opportunity for redesign in structure and objectives in the college of medicine was one of the positive dividends that resulted from the merger of the two medical professions in California in 1962 and the continuation of the California College of Medicine as a part of the University of California and as a major producer of physicians for this state.

The physical planning now involves termination of the long-standing affiliation with the Los Angeles County Hospital and a move (July 1 of this year) to the Orange County Medical Center (Orange County Hospital) where affiliation has now been achieved. The first buildings for the college on the UCI campus are being completed and some were occupied with the opening of school this September. Thus the college of medicine will function for several years with its basic preclinical sciences on the UCI campus and the nearby Orange County Hospital as its major clinical facility. Other hospitals in the area are important components of its total educational resources, namely, the Children's Hospital in

Orange, the Memorial Hospital of Long Beach, and the Veterans Administration Hospital in Long Beach. Other hospitals will be asked if they wish to join in this endeavor as more facilities are needed and as more students arrive.

Funds have already been requested for completing the basic instructional needs of a total medical school on the campus itself. A \$19,000,000 building of 360,000 square feet to house Medical Science I (preclinical sciences) has been approved. This is to be followed immediately with a development, for Medical Science II, of a 350-bed university hospital on the campus. Immediately thereafter, for Medical Science III, a clinical sciences building will be erected. That will complete the first basic requirement for a balanced medical educational program on the campus and its adjoining community resources.

Since the 150 acres that the college of medicine is on is visioned ultimately as a university health sciences center, plans are now under way for long range development programs. A planning committee for the health sciences is studying the proper sequence and broad desirable interrelationships in such matters as schools of dentistry, public health, veterinary sciences, graduate nursing and others, and the proper involvement for allied health professions training programs.

Thus is unfolding the astounding evolution of a new health sciences center at UCI. A center that is not only a part of a campus of a generous 1,500 acres, but with 150 acres earmarked for its development, is in a position to meet the physical needs of the medical and allied health sciences for the 21st century. Those demands will be massive indeed, since not only is it located in one of the most rapidly growing areas of California, having a projected population of 6 million by 1990, but it lies at the center of a massive megalopolis of the West Coast that ultimately must extend uninterruptedly from San Diego to Santa Barbara. With the prospects of such massive growth in an area of great prosperity and unexcelled climate and resources, there are few words that can adequately describe the prospects and exciting dimensions that lie ahead.

WARREN L. BOSTICK, M.D., Dean



The Scope and Responsibility of Medicine

A Forum with a Purpose

To engender discussion of what the scope and responsibility of medicine ought to be in today's society, CALIFORNIA MEDICINE printed in its June issue six essays by authors known to have keen if various interest in the subject.

In presenting the essays the editors expressed hope that they would be the beginning of a forum from which a definition of our profession's responsibilities may be distilled. Readers were invited to take part in a continuation of the forum in succeeding issues. Following are three contributions selected from those received to date. Others will be published in the months ahead.

If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102. Keep your essays short, please.

GLEN G. CAYLER, M.D.

Sacramento

THE IMPORTANT QUESTION it seems to me is not what is the scope and responsibility of medicine but *who* will organize and lead our communities, states, nation and world toward comprehensive health care including physical, mental and social health for all citizens of the world. I do not know who will eventually lead but it seems unlikely that it will be practicing physicians since as an organized group we have seemed more interested in the business of medicine rather than the profession of medicine.

How many of us lamented when the last President of the AMA opened and closed his reign by stating that the primary responsibility of organized medicine was the protection of the free enterprise system? How many obstetrical physicians pay direct or indirect attention to the social, mental and moral responsibilities of parenthood? How many pediatricians are leaders in initiating programs to improve imprinting and to lessen privation and deprivation during early infancy and to improve the opportunities for better family mental health? How many American physicians are even concerned that half the world is illiterate and hungry and dying from preventable diseases such as malaria and smallpox?

Our actions and inactions have led to our becoming businessmen and biological technicians and to our leaving the important leadership matters in regard to the scope and responsibility of medicine to others.

Unfortunately I see very little evidence that we will, or even want to, change. As evidence of our indifference is the fact that we still have not gotten around to eliminating racism in our own organization. Perhaps our hopes for a greater role in leadership lie in our obtaining fresh guidance and help from our present more community and social oriented students and young physicians and in our cooperating more actively with such organizations as the Medical Committee for Human Rights and the National Medical Association.

WILLIAM A. BELLAMY, M.D.

San Francisco

Associate Clinical Professor of Psychiatry, University of California, San Francisco, School of Medicine; and Past Chairman, Committee on Ethics, American Psychiatric Association

THE DEVELOPMENT OF Community Medicine in recent years is an innovation which few of us could foresee.

Similarly, it is difficult for most everyone to modify life-long patterns of thought in order to incorporate new ways of handling old problems. Community Medicine is no exception, and the current forum of CALIFORNIA MEDICINE should be most timely and welcome to all physicians and the many laymen these days who influence medical trends.

One aspect of Community Medicine is the increasing activities of governmental forces and societal philosophies advanced by countless social organizations—committees, and other groups who are pressing to be heard. They incorporate, into the scope of their hoped-for plans, many medical concepts that in prior years were traditionally considered to be the private domain of Medicine.

No longer can Medicine afford the blind paths of practicing in a vacuum. We need good laws on our statute books to back us up, and a hoped-for high level of ethical statesmanship—to replace present day deplorable politics—if ever the optimal level of medical potentialities are to be realized.

The following delineation of ethical responsibilities to the physician, attorney, and statesman are offered in the interest of fostering one further step toward drawing nearer to fulfillment of the medical potentialities of tomorrow:

1. Of the professional (physician, attorney, statesman) it is reasonable to expect that he develop those arts and skills necessary to effectively carry out his professional duties; that he acquire that degree of knowledge necessary to have something to profess; that he profess it with discretion; and that he develop that degree of moral fibre to profess it with sincerity, integrity, and a good conscience (ethics).

2. Of the law it is reasonable to expect that the law-makers continue their search for better laws toward our constitutional ideal of equal rights to everyone under the law; and that the practitioners of the law strive toward the ideals of the "professional man" as delineated above, in order to better implement these laws in the interest of justice.

3. It is reasonable to expect society to provide an optimal social milieu for the ideals expressed in (1) and (2) and that the political leaders maintain that political climate in which what the professional man has to profess will be heeded as at least one of the multiple alternative choices in planning our social order.

Our late President John F. Kennedy said, "Give me multiple choices," operating under a sound psychological principle expressed by Macauley: "Men are never so likely to settle a question rightly as when they discuss it freely."

JOHN B. DILLON, M.D.

Los Angeles

Professor and Chief, Division of Anesthesia, University of California School of Medicine, Los Angeles; and Chairman, Committee on Scientific Assemblies of the Scientific Board, California Medical Association

THE SCOPE AND RESPONSIBILITY of medicine in our present society would appear to be limitless. The lack of clear borderlines arises out of the concept that today "medicine" is not only responsible for the prevention and curing of disease but also for providing an environment of physical good health and mental well being. Indeed, this is a mandate.

In past years, the scope and responsibility of medicine was the scope and responsibility of the physician. It is clear that, because of the scientific, technical and sociological changes of the past decade, such an encompassing role for the physician is no longer possible or desirable.

Today, the physician is being forced by the pressures of our changing society to play a part, and only a part, in the scope of medicine. In the future, he will have to make a choice very early in his career as to what this part will be. Hopefully, however, this choice will not have to be made until such time as he has had sufficient background experience to make a value judgment. Today, the choice of career is frequently made too early but the effect is not as personally devastating as it may be in the future.

The physician will have many choices of career in the future, but all will be more demanding of technical and professional expertise than is required today. The pressure that society is exerting for evidence of continued clinical professional competency throughout a physician's career is something new, and has been an outgrowth of medicine's reputed successes. The pressure, by society, is being actively supported by the profession. This will almost inevitably require that if the physician is to be a qualified clinician he will have little time to be anything else. It will not be possible for very many to play multiple parts.

The future position of the physician as related to "medicine" and society is perhaps nowhere more forcefully and clearly stated than in the Report of the Royal Commission on Medical Education, April 1968, where the following appears on page 30:

"The social position of the doctor himself is also liable to change in important respects. As progress in science and technology continues, attitudes towards doctors, as towards members of other professions, are likely to move still further in the direction of regarding them as experts to be called in to prevent, investigate and remedy specific functional defects rather than as members of an elite who are accorded a special status by virtue of their general background and qualifications. The very fact that the doctor is concerned with the most personal aspects of human health, and indeed with the fundamental matters of life and death, will ensure a continuing high prestige for his profession; but the esteem in which the doctor is held by the community in general will be determined much more by his demonstrated competence than by the mystique of his calling. A separate but related development is the increasing need for the doctor to work in close cooperation, both in diagnosis and in therapy, with people who are not medically qualified—not only with the scientists whose contribution to clinical assessment is becoming increasingly important, but also with the many others who have important responsibilities for the patient both in ancillary services and in other capacities, and above all with the patient himself—a patient better informed and more interested in science and medicine than some doctors have often encountered hitherto. The leadership which the doctor often has to exercise has sometimes in the past appeared to be based on the assumption of a charismatic authority which has already ceased to be convincing and in the future will be completely inappropriate. The basis of the doctor's leadership will be his superior knowledge of the central facts of the clinical situation, his ability to exercise a decisive influence on the patient's illness, and his capacity to guide and co-ordinate the work of others whose cooperation is essential."

While the British system of health care is not ours, the above statement would appear to be equally germane to us and to our future role in the scope and responsibility of medicine.

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EDITORIAL

LATS and the Thyroid Gland

ELSEWHERE IN THIS ISSUE OF CALIFORNIA MEDICINE, Kriss presents his views on the long-acting thyroid stimulator of Graves' disease. This long known disorder almost begged for a fresh approach when in 1956, Adams, a New Zealander out of Sir John Hercus' great thyroid school, attacked with new zeal and derouted the pituitary:thyroid axis as basis for the continuing thyroid overactivity. The actual discovery in guinea pigs involved their repeated use for economy's sake and was so fortuitous as to recall the accidental bounties that came to the Princes of Serendip.

Kriss, among other points, presents the basis for considering LATS an antibody, of lymphocytic but not of monoclonal origin. He looks upon thyroid injury as important in pathogenesis to explain release of thyroid proteins as antigens inducing LATS as antibody. McKenzie, another authority on LATS, reviewed the same topic in *Physiologic Reviews*, January, 1968. Many similarities in viewpoints of the two are apparent. The careful student of the disorder will wish to read each. Similarities in position greatly exceed differences but the latter deserve comment. Thus, Kriss may be noted, in discussing the possible role of desiccated thyroid in precipitating Graves' disease, to speculate on the absorption of antigens and the consequent inducing of LATS antibody. McKenzie calls attention to the role of thyroxine itself, pos-

sibly acting to enhance LATS production by the lymphocyte. Either speculation may serve as a reminder that there is potential danger in the administration of thyroxine (and thyroid) and that specific indication should precede prescription of either. McKenzie's view may explain why induction of a period of health, as with an antithyroid drug, favors a lasting remission of the disease.

A more serious consideration of divergent views turns on noting Kriss to postulate that antigen: antibody complexes (thyroid proteins reacting with LATS) are of pathogenic significance in the ophthalmopathy of Graves' disease. McKenzie assigns no significance to LATS in the pathogenesis of ophthalmology. Kriss cites Catz, with other evidence, to bolster his position—Catz claiming total removal of the thyroid gland to benefit serious ophthalmopathy, presumably because the antigen is eliminated. (Kriss also notes Werner's dissent from Catz.) The important point for the practicing physician is that the role of LATS in ophthalmopathy remains under dispute and the role of total thyroidectomy for the eye disease is a matter for most careful and critical clinical investigation.

Much of the needed evidence about LATS which will guide physicians in the care of patients with Graves' disease remains to be gathered despite the signal advances of the past decade. A most urgent need is an experimental model of the disorder in which both hyperthyroidism and ophthalmic involvement occur. This development would carry a strong likelihood of enabling truly rational treatment of Graves' disease.

REFERENCE

McKenzie, J. M.: Humoral factors in the pathogenesis of Graves' disease, *Physiological Reviews*, 48:252-310, Jan. 1968.

Continuing His Education

THERE IS A GROWING FERMENT of professional and public interest in improving every aspect of health care. A particular concern is to make certain of the continued competence of practicing physicians and other health professionals in the present period of rapid scientific and technologic advances. In any circumstance and particularly in these times a physician who is responsible for the care of patients must maintain his competence and skills, and it is reasonable that there should be some assurance that this is in fact the case. The means by which this is to be done are now undergoing careful review; new and experimental techniques are being tried, and change is the order of the day.

The root problem, how today's practicing physician is to keep up-to-date, is not an easy one to solve. It takes about ten years to educate a physician and establish him in practice. At the same time, the body of medical knowledge doubles approximately in this interval and it has been aptly said that the half-life of a medical education is therefore only about ten years. Somehow in the face of all this a physician must keep up—or be kept up—in the interest of his patients' care. The matter is how? This becomes a most important question at a time when medical science is expanding by geometrical progression and the nation and the world face a shortage of practicing physicians for the foreseeable future.

Fortunately it is not necessary for every physician, or even any physician, to know all about every aspect of the art and science of medicine or to keep up with every step of medical progress. This being the case, it is necessary somehow to identify that new knowledge and those new skills which an individual physician should master, to effect their transfer into his awareness and to provide some evidence that this has been satisfactorily accomplished. The enormous complexities of this rather simply stated problem would suggest that perhaps some of the concepts in modern systems analysis might profitably be applied to promote the most efficient use of resources, be they the knowledge and skills of medical science, modern techniques for the storage and transfer of information, or the scarce spare time of the physician in a busy and demanding practice.

Since World War II there has been growing interest in these problems of continuing education for practicing physicians. It has gained momentum in parallel with recognition of the dramatic prog-

ress in medical science which began to take place during this period. This is the fourteenth year in which the *Journal of the American Medical Association* has published a comprehensive listing of postgraduate courses given throughout the nation. Both the California Medical Association and the American Medical Association have initiated programs to accredit those courses which meet certain standards. The American Academy of General Practice has made attendance at approved programs a condition of continued membership and this has proven an effective stimulus and satisfactory to the group. The American College of Physicians is experimenting with a confidential individual medical knowledge self-assessment program which attempts to identify for each physician where his knowledge is weak and to supply him with readily available references through which he can remedy his weaknesses. This program depends heavily upon the motivation of an individual physician for its success.

The California Medical Association also has a record of leadership in continuing education. Its Regional Postgraduate Institutes and Circuit Courses annually carry up-to-date information from major medical centers to physicians in more remote areas of the state. In its publication *What Goes On*, the Committee on Continuing Education of the Scientific Board brings current information concerning educational opportunities of all kinds to every physician in the state. Last year it held a "Planning and Goals Conference" which focused particularly upon the role of hospitals in continuing education and the problems of evaluation, motivation and accreditation or approval of courses or programs. As a result of this conference CMA has urged hospital medical staffs to require each staff member annually to list the courses he has attended. In cooperation with the Bureau of Research and Planning, this committee has conducted a survey of the attitudes and opinions of 2,600 California physicians. That survey is reported elsewhere in this issue (page 245).

All these activities are to be commended. They represent serious and responsible efforts to find answers to a most important problem. They should be continued and developed further. The stronger elements in the various approaches should be combined for greater efficiency and usefulness. But there is still a long way to go before this enormous problem is solved to the full satisfaction of either the profession or the public. It would seem that

this continuing educational process must somehow become more efficient. Among other things, this will require more attention to what new information needs to be disseminated to whom, and to the special educational needs of that most important recipient, the individual practicing physician. In addition, motivation of the busy physician and means to fill his needs must somehow be built in, together with suitable mechanisms to evaluate the effectiveness of the entire process.

The situation may realistically be viewed as one of an expanding universe of medical science in interaction with another expanding universe of demands upon the practicing physician for services to patients, other health professionals, the community, the state, the nation and, perhaps before we even realize it, the world. But in this expanding situation the number of hours in any doctor's day remains absolutely constant. This inescapable fact sharply limits what any physician can do in a day or even a lifetime, and emphasizes that not a moment of the time he can devote to his continuing education should be wasted.

Since each physician possesses a different body of knowledge and experience, it would seem logical that his program of continuing education should be individualized if his time for this purpose is to be used most productively. It therefore follows that the somewhat diffuse concept of "continuing education" for all physicians will necessarily evolve into a more specialized, even personalized approach emphasizing "continuing *his* education" for each practicing physician. This could and should be truly stimulating for all concerned.

Changing Concepts of Coronary Care

THE HIGH MORTALITY rate associated with acute myocardial infarction together with the development of reliable monitoring systems and effective resuscitative techniques stimulated the creation of coronary care units. The original concept of prompt resuscitation of patients in cardiac arrest proved to have limited therapeutic potential; most of the patients died. The recognition of premonitory signs of serious arrhythmia and the introduction of effective antiarrhythmic drugs and pacer-

makers has produced in recent years a shift in emphasis to prevention of life-threatening dysrhythmias. Several studies clearly document the efficacy of this approach.^{1,2}

However, mortality from acute myocardial infarction complicated by shock or severe heart failure remains distressingly high. Clearly, indices of myocardial function should be monitored in this group of patients. Many coronary units now are utilizing hemodynamic and biochemical measurements for assessing the degree of myocardial dysfunction as well as the response to various therapeutic programs. Such an approach, obviously, calls for an exceptionally skilled physician-nurse team.

The cornerstone of effective coronary care is this highly trained cadre of physicians and nurses. The nurses must be highly skilled in recognizing premonitory danger signals and should be empowered to initiate appropriate therapy. In this issue of CALIFORNIA MEDICINE, Stein and his associates report the need for trained personnel in established (or projected) units in California. Lack of the needed training may, in part, explain the observed under-utilization of nursing staff within some existing units. The need for properly trained personnel is an important community health priority and we applaud the efforts of the California Heart Association and the Regional Medical Programs* in expanding physician-nurse training programs to meet this need.

*Regional Medical Programs recently has approved three operational grants for the training of physicians and nurses working in Coronary Care Units. These grants have been awarded to Area 1 (University of California at San Francisco), Area 5 (University of Southern California), and Area 4 (University of California at Los Angeles).

REFERENCES

1. Lown, B., Fakhro, A., Hood, W. B., and Thorn, G. W.: The coronary care unit: new perspectives and directions, JAMA 199:188, 1967.
2. Killip, T., and Kimball, J. T.: Treatment of myocardial infarction in a coronary care unit, Amer. J. Cardiol. 20:457, 1967.

Doctrine In An Age of Science

A RECENT AND far reaching pronouncement of doctrine from across the sea invites thoughtful consideration of what is to be the place of doctrine from whatever source in a rapidly materializing age of science. Webster defines doctrine as "something that is taught: something that is held, put forth as true, and supported by a teacher, a school

or a sect.”* It is something of an article of faith, to be accepted without question or challenge. Doctrine in this definition has long been and still is part and parcel of many scholarly disciplines and of much human behavior. And it must be admitted that there is still much in medicine that is more doctrinal than truly scientific. But it is the genius of present-day science that sooner or later whatever is doctrine or theory or simply belief will be questioned, put to crucial test, and if found wanting either modified to fit the known facts or else cast aside.

Modern science is based upon a recognition of inherent order in the universe, an order which includes life itself. Scientific progress occurs when knowledge of this order is increased or when the capability of man to manipulate the order is improved. Science as we think of it today is still very young. Many of its disciplines remain cluttered with unsubstantiated doctrine or belief, but its progress is inexorable and the pace of this progress is certainly quickening. Science with its questioning of long accepted theories and beliefs and its gradually increasing comprehension of the universal order, is *the* fundamental fact of the modern world. It is unquestionably destined, and perhaps quite soon, to become the ground substance of human thought and belief and thus a major determinant of human behavior. As this occurs an age of science on this earth will come into full being.

This is certainly no time to throw stones. It was not so long ago that medicine considered a normal pregnancy to be an illness and treated it as such. Only recently has the success of early ambulation after a major operation overcome the doctrine that a prolonged period of rest in bed was needed. The routine anticoagulation of the blood after a suspected myocardial infarction is still doctrine in debate.

It would seem that the lesson to be learned from all this is that we must get on with the business of understanding the inherent order in life and in the universe, and then get on with the business of helping human beings adapt themselves and their earthly environment to the realities of this inherent order. Medicine, with the help of others in many walks of life, can do much to bring this about. As this is done the age of science will come to its full stature, and any doctrine which is not of the ground substance of science will be remembered only for its historic interest.

Guest Editorial

Vectorcardiography

VECTORCARDIOGRAPHY, TRADITIONALLY limited by the paucity of trained interpreters and the scarcity of the cumbersome equipment as well as the confusing welter of techniques employed, has come of age. Most of the limitations mentioned have been overcome and the technique has much to offer the internist and the general practitioner in his own community hospital, although at present the service is available in less than five percent of hospitals having fewer than 500 beds.

The vectorcardiograph itself has been reduced in size and complexity over the past ten years. Very satisfactory machines are available which are as small and compact as an electrocardiographic machine and light enough to be transported easily to and from the hospital by the cardiologist. Of several methods of recording the cathode tube image, the Polaroid® film technique seems to us the most convenient because the film is instantly available. The Frank method of applying the electrodes has been widely adopted in recent years owing to its simplicity and the relatively slight distortion. Since 1964 we have used this convenience to make vectorcardiography available to two non-teaching, so-called community hospitals, one of 100 and the other of 200 beds. Our experience over these four years suggests that vectorcardiography does indeed have something to offer in the interpretation of cardiac status. In our experience the procedure finds its greatest usefulness in the following situations:

- Where myocardial infarction is suspected but the scalar electrocardiogram is equivocal.
- In localizing infarction of the myocardium where the scalar electrocardiogram is “silent.”
- In evaluating chamber hypertrophy.
- In evaluating conduction abnormalities.

The procedure is of distinctly less value than the scalar electrocardiogram in the determination of cardiac rhythm.

The following situations are offered as practical applications of the manner in which analysis of the vectorial display on the oscilloscope can help the cardiologist in resolving the common, day-to-day dilemmas which confront him in the interpretation of scalar electrocardiograms. These examples are intended to be illustrative only and are obviously not intended as complete diagnostic criteria.

* (Webster's Third New International Dictionary—Unabridged.)

The Vectorcardiogram in Myocardial Infarction

1. The q Wave in Lead aVf

Every practicing electrocardiographer does daily battle with the problem of the significance of the q wave in leads III and aVf and frequently ends with the equivocal, "Old inferior infarction cannot be ruled out." Using the Frank technique, an initial superior force of greater than 0.025 seconds in the sagittal and frontal planes, while not infallible, affords greater evidence of the pathologic significance of the ubiquitous q aVf. An initial superior force of less than 0.02 seconds, while less diagnostic, affords some further evidence that the q wave in this position may not be significant.

2. The Small or Absent r Wave in Leads V_1 and V_2 (V_3)

This dilemma is another daily trial to the physician who interprets electrocardiograms in a hospital. The patient who has "poor r wave progression" across the precordium may have the residuals of an old anteroseptal infarction, or he may have a normal heart slightly rotated, or he may have nothing more serious than poorly applied test leads. In the Frank system the lack of an anterior force as manifest by a 0.02 second vector which is posterior to the main horizontal axis in the horizontal plane may be of considerable help in evaluating a very small or absent r wave in V_1 or V_2 and in V_3 . One must bear in mind, of course, that similar posterior orientation of the 0.02 second vector may also be seen in aortic stenosis, pronounced left ventricular hypertrophy, left bundle branch block and type B Wolff-Parkinson-White syndrome. But these ordinarily offer no confusion on the scalar electrocardiogram. The presence of a 0.02 second vector anteriorly in the horizontal and sagittal plane might help persuade the electrocardiographer that "poor r wave progression" may be positional.

3. The "True Posterior Wall" Infarct

Because the scalar electrocardiogram is essentially "blind" to the true posterior wall of the heart, the term *posterior infarction* has loosely come to include infarctions involving the diaphragmatic surface of the left ventricle. Although it is possible to suspect a "true posterior wall" in-

farct from a tall, wide r wave in V_1 , the diagnosis is very much abetted by a vectorcardiogram which shows a loss of posterior force and an exaggeration of anterior force in the horizontal and sagittal displays. Since right ventricular hypertrophy or Wolff-Parkinson-White syndrome can be confusing, careful analysis is necessary but the vectorcardiogram offers the possibility for diagnosis that simply does not exist in the scalar electrocardiogram. The term *posterior wall infarction* should properly be reserved for involvement of the true back of the heart, leaving the term *inferior wall infarction* or *diaphragmatic infarction* to describe involvement of the diaphragmatic surface of the left ventricle.

Myocardial Infarction Complicating Left Bundle Branch Block

Recognition of myocardial infarction in the presence of left bundle branch block is possible but difficult. The presence on the vectorcardiogram of a tiny initial posterior leftward force in a vectorial display which otherwise is characteristic of left bundle branch block is highly suggestive of infarction of the septum. It is this tiny initial posterior leftward force which is responsible for the characteristic q wave which may appear on the scalar electrocardiogram in V_6 . Unfortunately because of its inherent "low fidelity" this q wave is often masked on the conventional electrocardiogram.

Chamber Hypertrophy

The diagnosis of right ventricular hypertrophy in the presence of right bundle branch block is greatly facilitated by the examination of vectorial display where the characteristic patterns associated with these conditions are widely different, one from the other. The late, slow anterior rightward forces of a typical right bundle branch block can be easily and clearly differentiated from the early anterior and rightward forces of typical right bundle branch block.

It is to be hoped that the increasing convenience and availability of vectorcardiographic equipment and the repeated confirmation of the usefulness of the technique will encourage more cardiologists to familiarize themselves with it.

ARTHUR D. SILK, M.D.

A Survey of Continuing Medical Education for Physicians

Selected Findings Based on 2,600 Responses to Questionnaires

*A Socio-Economic Report of the Bureau of Research
and Planning, California Medical Association*

Summary of Findings

ALMOST HALF of all physicians say that they are usually or always satisfied with continuing medical education programs which they have attended. Excluding those who attend too infrequently to evaluate programs, the proportion who are satisfied is almost 60 percent. Most of those remaining state that they are sometimes satisfied with courses, while very few note general dissatisfaction.

Physicians express some difficulty in finding interesting programs which they can attend. The primary problem appears to be an inability to leave a demanding practice rather than an inability to locate programs. Time is a far more significant obstacle to attendance than are either costs or distances.

At least one physician in five attends formalized programs of continuing medical education so infrequently that he considers himself insufficiently informed to give an opinion on the subject. Physicians who do not attend are likely to be in the upper age ranges; however, some younger physicians, particularly in a few selected specialties, also indicated limited attendance at courses. Physicians in outlying areas are somewhat more likely to attend courses regularly than are their metropolitan-area peers.

Most physicians acquire the medical information which they need by attending two- or three-

day seminars or by reading texts and journals. Other modalities for transmitting medical information are generally considered by physicians as supplemental in nature with respect to their overall program of continuing medical education. This viewpoint may be attributed to any one or all of the following factors: (1) the limited scope of subjects with which they deal, (2) the fact that they are viewed by physicians as being of limited effectiveness, or (3) limited physician familiarity with them.

Specialty societies constitute the most highly valued type of agency under whose auspices continuing education programs are presented. Medical schools were ranked only slightly lower. Other agencies scored considerably below these two, with local medical societies last on the scale of values.

The Total Study

The foregoing summary briefly highlights most of the important findings contained in a recently published study, *A Survey of Continuing Medical Education for Physicians—Part I*.^{*} Selected findings based on an analysis of 2,649 questionnaires completed by physicians throughout California are contained in Part I; a subsequent publication will provide further results of the study, including

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This survey was conducted by the Bureau of Research and Planning on behalf of the Committee on Continuing Education of the California Medical Association under the auspices of the California Medical Education and Research Foundation.

Reprint requests to: CMA Bureau of Research and Planning, 693 Sutter Street, San Francisco 94102.

TABLE 1.—*Evaluation of Effectiveness of Continuing Medical Education Courses, by Selected Physician Characteristics*

Physician Characteristic	Evaluation (percent of total)			
	Usually or Always Satisfied	Sometimes Satisfied	Usually or Always Dissatisfied	Attend too Rarely to Evaluate
Specialty Grouping:				
Medical Specialties	46.4	38.2	2.9	12.5
Surgical Specialties	48.8	30.5	0.4	20.2
General Practice	56.7	29.0	1.4	12.9
Other Specialties	35.0	31.0	1.2	32.8
Type of Area:				
Metropolitan	47.7	31.8	1.4	19.1
Non-Metropolitan	58.0	29.4	1.4	11.7
Age Group:				
37 and under	45.6	36.4	0.9	17.0
38-47	47.6	33.1	2.0	17.4
48-57	49.4	32.1	1.2	17.4
58-67	51.8	24.4	0.9	22.8
68 and over	54.7	12.9	0.1	32.3
American Board Certification:				
Certified	42.6	33.1	1.2	23.0
Not certified	52.7	30.5	1.5	15.3
Not certified (specialists only)	47.8	32.4	1.6	18.2
All Physicians	48.5	31.6	1.4	18.5
TOTAL NUMBER OF PHYSICIANS	11,765	7,659	337	4,491

an enumeration of medical subject areas which physicians think should be given more attention.

This *Socio-Economic Report* contains some details about the findings. While the summary provides highly condensed data about all portions of the questionnaire which have been interpreted thus far, space limitations permit discussion of only a few of the more important findings in the subsequent text of this report.

Effectiveness of Courses

Table 1 reveals how practicing physicians evaluate the effectiveness of continuing medical education courses as they are now functioning. Each respondent was asked to check one of four possible statements which most closely approximates his own opinion; the first three statements ranged from "usually or always satisfied" to "usually or always dissatisfied" with courses, while the fourth statement was designed for those physicians who feel that they attend courses or programs too infrequently to make an evaluation.

Most physicians are "usually or always satisfied" with courses.—Almost half of all physicians (48.5 percent) are at least "usually satisfied" with courses. A rather large segment (31.6 percent) are only "sometimes satisfied," while an almost negligible proportion (1.4 percent) indicated that they are "usually or always dissatisfied." The remainder

(18.5 percent) said that they do not attend programs with sufficient frequency to present an opinion about their satisfaction. If this final group which expressed no opinion were excluded, the proportion expressing maximum satisfaction would rise to approximately three in five. There appears to be little doubt, however, that dissatisfaction is a contributing cause of non-attendance; the extent of this relationship will be tested in subsequent questioning of physicians.

Figures concerning physician satisfaction must be interpreted cautiously. There are indications that the proportion who do not attend programs is at least somewhat understated; further analysis is currently being done to evaluate whether this is the case and, if so, to what extent. In any event, these data provide some insights into physician opinion about currently available programs of continuing education.

The table also classifies satisfaction and attendance statistics according to four broad medical specialty groupings, type of geographic area, age and American Board Certification. These groupings can provide insight into factors which relate to physicians attendance at, and satisfaction with, programs of continuing medical education.

Medical men, general practitioners attend regularly.—Physicians in medical specialties and in general practice are generally more likely to attend

programs than are physicians not included in such groups. Seven out of every eight physicians in each of these two groups attend with sufficient regularity to have given an evaluation. On the other hand, under four out of five surgeons and just over two out of three physicians in "other" specialties attend programs often enough to evaluate them; among surgeons and "other" specialties, there is considerable internal variation in the proportions who do not attend courses. Physicians in neurosurgery, otolaryngology and plastic surgery are the least likely to attend programs; over half of all psychiatrists do not attend courses often enough to evaluate them. (Specific details such as figures for individual specialties are contained in the larger study.)

Satisfaction level varies among the specialties.—General practitioners are most likely to have specified that they are "usually or always satisfied" with courses they attend. Surgeons are also usually satisfied and are least likely to have registered total dissatisfaction. There are, however, considerable variations among individual specialties within the general field of surgery.

Although the group of physicians in medical specialties who indicated *usual* satisfaction is larger than the group who said that they are only *sometimes* satisfied, an above average proportion of physicians in medicine (2.9 percent) registered total dissatisfaction. These were primarily internists. Of the two-thirds of physicians in "other" specialties who attend programs, there is a very close split between those who were usually satisfied and those who were only sometimes satisfied. Among psychiatrists, dissatisfaction among those who attend is high and undoubtedly accounts in part for the large size of the group who do not attend programs. Individual "other" specialties in which a relatively high degree of satisfaction is shown are anesthesiology, pathology and neurology.

Attendance levels, satisfaction are higher in outlying areas.—Physicians in non-metropolitan areas attend programs more regularly than do their peers in metropolitan areas and, when they do attend, are somewhat more satisfied. There is some association between these figures and the fact that the proportion of physicians in general practice is higher in outlying areas of the state.

Younger, board certified physicians less easily satisfied.—There is little doubt that younger physicians are more demanding of courses and are

more apt to be only sometimes satisfied. The table also indicates a marked decline in attendance at courses as physicians approach age 60 and a further decline in the next higher age group. It is likely that the decline in attendance actually begins at a somewhat earlier age, since physicians who may not have attended courses in a few years might still be willing to evaluate them on the basis of past experience.

Physicians who have board certification are generally more difficult to please than those without certification. Among board certified physicians, only 42.6 percent said that they are usually or always satisfied with courses, while 52.7 percent without certification indicated this high level of satisfaction. Among specialists only, 47.8 percent of non-certified physicians are usually satisfied.

Another interesting point is that those physicians without board certification are more likely to attend courses regularly than are physicians with certification. This difference is to some extent associated with the pattern which emerged between general practitioners and specialists, since figures for physicians without certification are affected by the inclusion of general practitioners. Among specialists only, however, a comparison of figures for those who are board certified and those who are not indicates that, in general, certified specialists are not only more difficult to satisfy, but also attend with less regularity than those without certification.

Availability of Programs

Table 2 provides some insights into the question of how frequently physicians are able to find continuing education programs of interest *and* to attend them. These data are classified according to medical specialty grouping and by response to the prior question about satisfaction with courses.

Respondents encounter difficulties in attending programs.—Among all physicians, almost half (47.2 percent) said that although they are able to find interesting programs, they are often unable to attend them. This response may indicate one or both of the following problems: (1) physicians feel that the demands of their practices preclude attendance at such programs, or (2) programs are given at the wrong times or places. The first problem is outside the scope of this study; the second will be discussed in connection with information contained in Table 3.

General practitioners are most likely to find

TABLE 2.—Frequency with Which Physicians Find Programs of Interest and Are Able to Attend, by Selected Physician Characteristics

Physician Characteristic	Statement (percent of total)			
	Often Find Interesting Program and Can Attend	Occasionally Find Interesting Program and Generally Can Attend	Find Interesting Programs, Often Unable to Attend	Rarely Find a Program of Interest
Medical Specialty Grouping:				
Medicine	24.6	22.2	51.8	1.5
Surgery	27.6	21.9	44.1	6.3
General Practice	35.0	18.8	44.9	1.3
Other	15.0	17.6	52.7	14.4
Evaluation of Programs:				
Usually or always satisfied	43.3	15.9	39.3	1.5
Sometimes satisfied	17.8	36.2	45.6	0.4
Usually or always dissatisfied	12.2	32.6	36.5	18.7
Attend too rarely to evaluate	2.0	4.0	71.5	22.5
All Physicians	27.2	20.3	47.2	5.3
TOTAL NUMBER OF PHYSICIANS	6,592	4,927	11,446	1,287

programs of interest which they can attend, while physicians in "other" specialties (primarily psychiatrists, pathologists, and anesthesiologists, according to detailed data contained in the full report) are least likely to find programs. When grouped, the proportion of physicians in medical and in surgical specialties appear to be approximately equal in their likelihood of finding programs. The fact is, however, that the three major medical specialties show an extremely high degree of internal consistency on this subject, while the variation among individual surgical specialties is extremely wide.

Some surgeons can't find programs; others can't leave practices.—Among surgeons, relatively large proportions of ophthalmologists, for example, are able to find interesting programs and attend them, while neurosurgeons and otolaryngologists are considerably less able to do so. For neurosurgeons the problem appears to be finding interesting pro-

grams, while for otolaryngologists it appears to be primarily the inability to attend them. Surgeons in two other numerically small specialties (colon and rectal surgery and plastic surgery) are unlikely to find programs of interest, while almost no general surgeons, obstetrician-gynecologists, ophthalmologists or orthopedists indicated problems in locating interesting programs. Non-attendance among physicians in medical specialties is also entirely attributable to the inability to attend rather than to the inability to find interesting programs.

Satisfaction level shows association with ability to find programs.—Two patterns emerge from the second group of figures appearing in Table 2, a comparison of frequency with which physicians find interesting programs that they can attend and satisfaction with these programs. The first relationship indicates that physicians who are generally satisfied with programs seem to have greater success in locating interesting programs than do those

TABLE 3.—Barriers to More Frequent Attendance at Continuing Medical Education Courses, by How Frequently Physicians Find Programs of Interest

Barrier to More Frequent Attendance	Frequently Finding Programs of Interest (percent of total)				
	All Physicians	Often	Occasionally	Often, But Can't Attend	Rarely
No Barrier Indicated	12.1	21.8	15.2	2.3	37.8
Time (only)	33.3	32.6	31.8	35.3	26.1
Locale (only)	3.4	3.5	4.0	3.2	3.0
Costs (only)	8.6	8.3	11.9	7.1	10.9
Time and Locale (only)	15.3	13.9	16.1	15.8	15.9
Time and Costs (only)	16.4	14.3	9.8	21.7	4.7
Locale and Costs (only)	3.9	1.4	6.7	4.4	0.9
Time, Locale and Costs	7.0	4.3	4.6	10.3	0.9
Total Mentioning "Time"	72.1	65.1	62.4	83.1	47.5
Total Mentioning "Locale"	29.7	23.1	31.4	33.7	20.6
Total Mentioning "Costs"	35.8	28.3	33.0	43.5	17.2

who are only sometimes satisfied (43.3 vs. 17.8 percent *often* find interesting programs while 15.9 vs. 36.2 percent only *occasionally* find them). The second is that a preponderance of physicians who attend programs too rarely to evaluate them attribute non-attendance to the demands of their practices (71.5 percent) rather than to an inability to find interesting programs (22.5 percent).

Barriers to Attendance

Physicians were asked to indicate reasons why they do not attend as many programs of continuing education as they might like to attend. Barriers to maximum attendance such as time, locale of programs and costs (including loss of income) were suggested; physicians were invited to check all that they considered applicable. The pattern of responses can be seen in Table 3.

Few can attend as many programs as they would like.—Among all physicians, slightly less than one in eight (12.1 percent) did not check any of the barriers suggested, thus implying that there is nothing to prevent them from attending programs as often as they like. Understandably, such physicians were relatively more prevalent among those who often find interesting programs which they can attend; nevertheless, even among this group, just 21.8 percent indicated no barriers. Of those who rarely find an interesting program, the prevalent problem appears to be lack of interest in programs presented rather than considerations of time, locale or costs; over three in eight of these physicians (37.8 percent) did not check any barriers.

Time problems keep physicians away from programs.—The most frequently noted reason for limited attendance was time. Over seven physicians in ten (72.1 percent) indicated that they would attend more courses if time permitted. Of these, about half indicated that time was their *only* problem, while the remaining half said that one or both of the other factors also tended to limit their attendance.

Costs, distances are less important deterrents.—Next in importance was the element of costs. Slightly over one in three (35.8 percent) mentioned costs. Of this third, approximately one in four (8.6 percent) checked this as the *sole* barrier to more attendance; most physicians who find costs to be a deterrent also expressed concern about time away from practice.

Locale was the least important problem for

respondents, in terms of numbers who are affected by this consideration. Very few indicated that this was the only barrier to greater attendance; of the total 29.7 percent who specified locale, only 3.4 percent specified nothing else. The remaining 26.3 percent indicated other problems, particularly that of time.

Even those physicians who often find interesting programs which they can attend generally specified that they would attend more programs if it were not for the reasons indicated on the questionnaire. Almost two-thirds of this group specified time, while smaller proportions checked costs and locale. As already mentioned, fewer physicians among those who rarely find courses of interest checked any of the problems suggested. This is understandable, since barriers such as time, costs and locale are of considerably less importance to physicians who are generally unable to locate interesting courses *at all* than to those who find them but are unable to attend.

Physicians who seldom attend blame their busy practices.—Some helpful comparisons can be made among the four "frequency" categories. While time is the most important deterrent among all groups, it accounts at least in part for almost five out of six physicians (83.1 percent) who experience the problem of finding courses and being able to attend them. The relatively small increase in the percent among this group mentioning locale, compared with all physicians, suggests that the problem of distance is easier to solve than that of time. Costs, however, are a relatively important component of the problem of those who attend courses only infrequently.

Time is less a factor among those who only occasionally find interesting programs than among those who often find them and attend; on the other hand, the problem of locale increases markedly between those who often find interesting programs and those who find them only occasionally. The former relationship suggests that there is a group of physicians who find too many courses to be able to spare time for them all; the latter relationship suggests that there are many physicians living outside of major metropolitan areas who only occasionally find interesting programs and can't get to them because of distance.

Evaluation of Modalities

Respondents were requested to rate nine individual modalities employed in the field of con-

TABLE 4.—Mean Ratings* Given to and Percentage of Physicians Familiar with Selected Modalities Employed to Transmit Medical Information, by Medical Specialty Grouping
(Rating Scale: 1=least valuable, 4= most valuable)

Modality	Medical Specialty Grouping									
	All Physicians		General Practice		Medicine		Surgery		Other	
	Mean Rating	Percent Familiar	Mean Rating	Percent Familiar	Mean Rating	Percent Familiar	Mean Rating	Percent Familiar	Mean Rating	Percent Familiar
Two- or three-day symposia	3.5	92.4	3.5	90.7	3.4	93.9	3.5	95.0	3.4	89.5
Bedside postgraduate courses in medical schools	2.5	52.5	2.8	56.1	2.5	53.2	2.3	53.2	2.2	43.6
One- to three-week in-service programs	2.5	44.9	2.5	41.1	2.5	41.3	2.5	50.3	2.5	47.6
Three- to six-month traineeships in teaching institutions (funded)	2.7	42.1	2.5	35.8	2.9	39.0	2.6	47.5	2.9	48.6
Hospital grand rounds and clinics	2.6	66.1	2.6	59.9	2.8	75.2	2.6	70.3	2.3	59.1
Hospital TV conferences from medical schools	2.2	63.4	2.5	63.2	1.9	61.6	2.1	68.0	2.1	58.7
Hospital radio conferences from medical schools	1.7	50.5	1.9	47.9	1.5	49.5	1.5	56.3	1.6	47.2
Audio-digest tapes	2.3	61.7	2.4	56.6	2.3	60.0	2.2	70.0	2.5	59.3
Textbooks, journals, etc.	3.0	89.2	2.7	86.4	3.1	91.2	3.2	89.8	3.2	91.0

* Means calculated excluding modalities with which respondents were not familiar.

tinuing medical education, according to their effectiveness in transmitting information to physicians. Mean ratings and proportions of physicians familiar with each modality, among all physicians and by specialty grouping, are shown in Table 4.

Although valuable information can be gleaned from an analysis of the data which were provided by responses to this question, some problems should be borne in mind when the information is interpreted. Physicians were asked to rate *all* modalities with which they are familiar, using a scale of 1 = least valuable, 4 = most valuable; they were to leave blank modalities with which they are unfamiliar. Regrettably, some respondents rated only those modalities which they consider valuable; others incorrectly interpreted the instructions and rated only four of the modalities, assigned a 4- 3- 2- 1 scale of values. The results of these two inaccuracies are the following: (1) an overestimate of the proportion of physicians who are unfamiliar with various modalities, particularly those which are supplemental in nature, and (2) a somewhat inflated mean rating attributed to the less familiar modalities (unrated modalities were excluded from calculation of means).

Two- or three-day symposia rate highest.—Data contained in Table 4 show that among all physicians, two- or three-day symposia are considered the most valuable modality for the transmission of medical information. Almost all physicians are familiar with the modality and 58.7 percent of them gave it the top rating of 4. Next in value rating came textbooks and journals; the mean rating given was 3.0. Three- to six-month trainee-

ships in teaching institutions rated next (with a mean rating of 2.7); then came hospital grand rounds and clinics (2.6) and a tie between bedside postgraduate courses in medical schools and one- to three-week in-service programs (2.5). Lowest rated were hospital radio conferences from medical schools (1.7); TV conferences and Audio-Digest fared slightly better (2.2 and 2.3, respectively). It should be noted that relatively low ratings which were accorded to specific modalities do not necessarily indicate that they are unimportant, but rather that, measured against the total spectrum of methods employed within the field of continuing medical education, they are possibly of supplemental or marginal value. It does not preclude the possibility of their being quite valuable when employed to transmit specific types of information.

Physicians show little familiarity with some modalities.—Most familiar to physicians are two- or three-day symposia and textbooks or journals. Substantial proportions, however, did not give ratings to the following modalities: three- to six-month traineeships in teaching institutions, one- to three-week in-service programs, radio conferences, and bedside course in medical schools. Of these four modalities, all but radio conferences were considered rather important by those who were familiar with them. As noted above, the proportion of physicians familiar with each modality is probably understated somewhat.

There are a few differences among the four grouped specialty classifications which exist and are important with reference both to evaluations and to physician familiarity with them.

General practitioners like bedside courses, radio and TV conferences.—General practitioners generally gave higher than average ratings to bedside postgraduate courses in medical schools, and to both hospital TV and radio conferences from medical schools. They gave below average ratings to long-term traineeships in teaching institutions and to textbooks and journals. There was generally a somewhat less than average amount of familiarity among GPs with the variety of modalities indicated on the questionnaire; an exception to this is the bedside course in medical schools, with which general practitioners are generally better acquainted than are physicians in most other specialties.

Medical men like long-term traineeships, grand rounds.—Opinions among physicians in medical specialties do not vary greatly from those expressed by all physicians. There was some tendency to find long-term traineeships in teaching hospitals and hospital grand rounds and clinics more valuable; both radio and television conferences from medical schools were given below-average ratings. Medical specialists are considerably better acquainted with grand rounds and clinics, somewhat less well acquainted with one- to three-week in-service programs and with three- to six-month traineeships.

Surgeons are acquainted with most modalities.—Opinions among surgeons also parallel those of the total group fairly closely. The only instructional technique which surgeons generally regard more favorably than do other physicians is the printed word. Conversely, they draw somewhat less satis-

faction from bedside courses in medical schools and from hospital radio conferences. Surgeons demonstrated an exceptional degree of familiarity with all modalities. Among the modalities with which surgeons showed a particularly high degree of familiarity were Audio-Digest tapes, hospital radio and TV conferences, and medium- to long-term traineeships or in-service programs.

Further data needed to analyze physicians in "other" specialties.—Because of the diverse nature of specialties contained in the "other" category, it is difficult to make generalizations. There are three modalities which these physicians rate higher than do other physicians; long-term traineeships, Audio-Digest tapes, and reading materials. At the other end of the scale, two similar types of modalities are rated well below average—bedside postgraduate courses in medical schools and hospital grand rounds and clinics. It should be pointed out that physicians in "other" specialties are also less familiar with these two modalities, while they tend to be more familiar with in-service programs and traineeships. These figures are weighted highly by psychiatrists and anesthesiologists.

The entire subject of modality evaluation demands more investigation. An initial step will be the analysis of effectiveness evaluation and familiarity patterns within each individual specialty. Further investigation being conducted among non-respondents to the original questionnaire approaches this specific subject somewhat differently and will provide additional data about the subject.

Continuing Education for the Specialist

LEON P. FOX, M. D., *San Jose*

■ *Specialists are having many difficulties defining and developing more effective methods in the area of continuing medical education. Present unorganized multifaceted mechanisms are too little utilized by the majority to be acceptable. A cooperative effort by parent specialty organizations, accredited hospital staffs and the State Board of Medical Examiners could explore the possibility of establishing standards by which a qualitative and quantitative review of the level of performance of physicians could be done. The initiative must be exercised by these groups to forestall governmental intervention.*

IN THIS ERA, there is general uneasiness with regard to medical education in general, particularly continuing education in special fields of practice. Much is being written about the needs in this area and innumerable ideas have been propounded to solve the problem, but there is no coordinated effort being made by a practical pilot study to prove the effectiveness of any plan, at least not in this geographical area.

Many of us depend upon crude methods of keeping ourselves up to date in knowledge of drugs, diagnostic modalities, technical changes, medical and surgical management and preventive procedures. The gap between town and gown, the reluctance of practitioners to take time to improve competence, and the severe lack of time leaves us struggling in a sea of confusion. Although I utilize my own specialty of obstetrics and gynecology to explore the problems relating to continuing education and suggested solutions, it is apparent that the discussion is applicable to all specialties.

Continuing medical education for obstetricians-gynecologists concerns at least three groups of

physicians, the practicing obstetrician-gynecologist, the teaching obstetrician-gynecologist and the family practice obstetrician-gynecologist. As in other disciplines, the explosion of scientific knowledge in health care in our field has been as phenomenal as the population explosion and as difficult to cope with. Keeping "refreshed" while overly busy providing health care is becoming very arduous and much needs to be done to organize methods which will be practical and usable.

Present Methods

At present we depend upon many "self helps" to keep us up to date—hospital conferences, periodic seminars and assemblies, medical association scientific sessions, national and regional specialty colleges and postgraduate programs.

The "self helps" include the use of the voluminous supply of periodicals in our own specialty as well as closely allied disciplines. Each year we are afforded approximately 1,900 pages of current opinion in our green journal, *Obstetrics and Gynecology*; 3,600 pages in the gray journal, *American Journal of Obstetrics and Gynecology*; and innumerable pages in various abstract publications such as the *Survey* which has some international

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Reprint requests to: 303 North Fifteenth Street, San Jose 95112.

flavor. The British, the International Federation and other foreign journals are readily available to most of us. The more highly specialized material in fertility, endocrinology, cancer and other subjects provides information to a more limited group.

California Medicine and the *Journal of the American Medical Association* are more diversified but do appear on our desks regularly with another 5,500 pages of yearly effort by authors in varied fields.

Reading material only has value when it is properly read—a fact which I am afraid lessens its effect as a refresher. With such a tremendous supply available, many depend upon summary scanning, which is inadequate.

Another “self help” modality of continuing education is the perennial supply of Audio-Digest tapes provided for us by a subsidiary of the California Medical Association. Selected subjects by authoritative discussants find wide use by generalists and by colleagues in our own specialty.

Hospital conferences in community institutions frequently are limited to the required cursory review of the accumulative clinical material of the preceding month supplemented by periodic guest speakers, usually oriented to general practitioners or to house officers. Teaching institutions provide more sophisticated presentations at grand rounds and didactic conferences are of great value in keeping staff members up-to-date. Many community hospitals have annual symposia with visiting professors offering presentations more generally oriented and thus of only occasional benefit to our section.

Periodic seminars and assemblies such as regional meetings sponsored by the state medical associations and the universities attract interest widely over our state and others, but are often too diversified. The Assembly and Forum of Southern California is an intensified effort to bring international authorities with current opinions to a significant proportion of us each year.

Obstetric-gynecologic sections of state and national associations have annual and semi-annual programs of limited interest which are not well attended and could not be a dependable sole refresher.

The most rewarding experience in our continuing education is the regional and national meetings of the American College of Obstetricians and Gynecologists and the American College of Surgeons. Each has formal postgraduate programs,

discussions on investigative work, roundtables, conferences and many variable attractions including televised live clinics and surgical demonstrations, plus numerous exhibits.

Postgraduate efforts of our medical schools continually offer in-training to those who wish to brush up or become enlightened in special techniques and make studies in depth of new knowledge.

All of these mechanisms are being used by a relatively small proportion of obstetrician-gynecologists and there is no assurance that those most in need are being exposed effectively to them. It is the individual's choice and his own conscience that determines the degree of his participation.

Why, then, should we concern ourselves with continuing medical education since it is available to us to choose and use as we will?

Demands for Change

The interest has increased for many reasons and there is a growing demand for control and accurate evaluation by the medical profession, government and other segments of society. Planners for health care in and out of organized medicine view the aging doctor of medicine as one who persists in the practice and teaching beyond his time of astuteness and physical ability. It has been long felt that some restrictions should be applied in this area. We know that chronologic age alone is a very fallacious guideline to follow and as yet proper mechanisms have not been developed which would determine the senior physician's ability.

The continuing use of outmoded practice indicated by routine subtotal hysterectomy, the combined abdominal with vaginal approach to prolapse, Watkin's interposition operations, frequent use of classic cesarean section, and homeopathic antibacterial therapy for septic conditions identifies the hermit pelvic surgeon who has not improved his knowledge in this field since World War II. These patterns often develop early in one's career and are even sometimes exemplified by the young specialist who finishes his training, completes his military obligations, quickly becomes busy and isolated from exposure to the rapid advances and seldom returns to the mainstream.

The present system of assuring continuing medical education seems inadequate when we view the rapid advances in our field. There is much need for an orderly plan which would guarantee not only exposure of all of us to such current knowl-

edge, but would evaluate the effectiveness of the system.

Organized medicine through our county, state and national associations is constantly studying, developing and applying various techniques, theories and attractions which would involve every physician in some refresher experience. The American College of Obstetricians and Gynecologists has pioneered the system of continuing education for its own members and has worked with the American Academy of General Practice to improve the standards of practice in its field. The leaders have done this because of the founding principles which make the College responsible for our continuing education; and other organizations have offered cooperation to help carry out the task. In fact, the College is carrying out the demands of the members of our specialty to establish and maintain standards of continuing postgraduate education in this field.

All obstetrical-gynecological societies in California and this region of the United States, including our own San Francisco society, the Pacific Coast society and others, base their reason for existence on the premise of improving standards of practice and so require their members to remain current in all aspects of knowledge in our specialty. There is an increasing hunger for new information by the majority in our discipline.

National and state "Medicare" laws have indicated a demand for better health care of the senior citizens and the medically indigent throughout the country. Those who give substandard care are being identified by review committees in our communities and they are being removed as purveyors of medical service to these people. Regardless of agreements and contractual arrangements, it will remain a truism that he who pays the fiddler will call the tune, and government will make competence surveys mandatory.

The Board of Medical Examiners, working with the deans of medical schools, insurance carriers and the California Medical Association, has recognized a growing need for evaluation of the grass-roots standards of practice among physicians and is studying the methods by which each individual doctor of medicine can be screened as to his ability to continue practice with or without restrictions.

Although we all abhor governmental control, whether state or national, we do enthusiastically accept the necessity in other areas such as control over safety of airline and other public carriers or

even the high standards required when we seek our license to practice. Periodic recheck on the latter is what the Board of Medical Examiners will demand if a better solution is not forthcoming.

Trial lawyers and the courts are bringing more and more pressure upon the physician witness or defendant to show his grasp of new medical ideas and prevalent practice. Thus, the malpractice and forensic considerations also make continuing education imperative.

Many observers believe alternative methods by the state can be formulated in a more practical manner than examinations, undercover reports or other distasteful methods.

Suggested Mechanisms

If appropriate committees of all accredited hospitals were required to make reports on staff physicians periodically to the Board of Medical Examiners, a realistic level of performance of the majority of our practitioners would evolve. Other methods would be needed for physicians practicing in small hospitals and outlying areas.

The American Board of Obstetrics and Gynecology, which is under the control and jurisdiction of the American Medical Association, has never undertaken reevaluation of its diplomates once they are certified. This is true of the American College of Obstetricians and Gynecologists and the American College of Surgeons. Potentially, all three offer many possibilities of including certification review within their purview.

The American Academy of General Practice was organized on the premise of establishing and maintaining a system of requiring continuing education for all its members. A specific quantity of documented quality postgraduate work over a stated period is required in order to maintain membership in the organization. This of course does not interfere with the licensed right of physicians to practice, but experience has shown that few physicians choose to lose their membership in the Academy for failure to do the required postgraduate study. It is not, then inconceivable that the American Colleges and/or the American Boards might arrive at a common standard of requirements for postgraduate education and insist that their members offer periodic evidence of fulfilling their obligation. This mechanism was recently submitted by John B. Dillon, M.D., of UCLA. He suggested that evidence of compliance be appended to one's license and that it be available to patients

as well as to surveyors. He pointed out that re-examination by the Board of Medical Examiners would be unreasonable, impractical and perhaps of minimal factual value. Reexamination by the Colleges and others would similarly be of questionable effectiveness.

The new public law concerning heart disease, stroke and cancer makes possible cooperative arrangements improving the care of persons with these diseases. This development concerns our specialty (in at least one facet) and deserves some consideration. Mr. Paul Ward, executive director of the California Regional Medical Program, has described efforts to stimulate local participation and determination of local needs by the men and women most directly concerned with meeting them. For planning purposes these locally determined needs are to be aided by administrative staffs of the eight medical schools in California. These efforts will, no doubt, bring about evaluation of various levels of professional ability in the communities served throughout the California region, which includes the Reno-Sparks-Carson City and Las Vegas areas of Nevada.

In the past, medical schools and teaching hospitals have been similar to the Board of Medical Examiners and other certifying organizations in that they give the blessing of competence to the graduate and rarely have the opportunity to keep track of the physician they have produced, or to attract his attention to continuing education. There is no functioning method, at this time, of assuring society that obstetricians-gynecologists and practitioners in other branches of medicine and surgery are continually maintaining their professional competence.

It seems obvious that if we as a profession do not develop a working mechanism and activate it promptly, then the state will surely do so in an

arbitrary manner. Our College has the means and motivation to do this and it is incumbent upon the Fellows to urge a trial plan in our state by working with the Board of Medical Examiners to obtain acceptability.

Conclusion

It is apparent that current methodologies of continuing education for specialists are undefined, poorly organized and inadequately utilized for present and future effectiveness. Guidelines should be developed in each specialty, at the level of a non-arrogated parent organization, which would outline the requirements and minimal standards of those in that field. It would behoove the practitioner to be continually informed of new knowledge and techniques in his own chosen way, and his acumen would be measured by quantitative and qualitative credit earned in a specific period of time.

Concurrently, periodic reports from departmental committees of all accredited hospitals utilized by the physician, similar to the reports now required by the American Board of Obstetrics and Gynecology for applicants, should be obtained to complete the evaluation. These two basic mechanisms could be activated every fifth year and serve a useful purpose. I feel sure the Board of Medical Examiners would cooperate. Even physicians who are reluctant to stand the test of competence would more readily accept a method such as this than governmental decree.

BIBLIOGRAPHY

Hodgkinson, C. P.: Continuing education in gynecology-obstetrics, *Obst. & Gynec.*, 18:243, 1961.

Dillon, J. B.: A mechanism to assure continuing medical education, *Calif. Med.*, 106:235, 1967.

Ward, Paul: Heart-Stroke-Cancer (Public Law 89-239). Address before Santa Clara County Medical Society Membership, Palo Alto, 27 April 1967.

California Medical Association



Council Highlights

Highlights of the Actions of the California Medical Association
545th Council Meeting, June 14 to 15, 1968, San Francisco

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA Headquarters office.

CMA Activity in State Public Health matters was affirmed by Council when after discussion and amendment the following actions were taken pursuant to written recommendations presented by Dr. Carl Anderson:

- Voted to reaffirm the policy position that physician and county society involvement and participation in the "Partnership in Health" activities at the local level is of the utmost importance.

- Voted to adopt a policy statement that the public health of the people of California is a primary and continuing concern of the CMA and the physicians of California and to continue to implement this policy by seeking appointment of knowledgeable physicians on governmental boards, commissions and committees dealing with health and related problems.

- Voted to request California Blue Shield to explore the feasibility of serving as fiscal agent or on a prepaid basis for the administration of the

Crippled Children's Services and other state administered medical care programs and sponsor appropriate implementing legislation if such a proposal is found to be feasible.

- Voted to encourage the Office of Health Care Services to establish and use a medical advisory

MALCOLM C. TODD, M.D. President
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committee to guide the office in the day-to-day administration of utilization controls, prior authorization, county consultant activities and related activities.

- Voted to adopt a policy position that schools of public health should be closely integrated with schools of medicine and the allied health professions, and to encourage the Scientific Board and the deans of the schools involved to strive for such an integration.

- Voted to charge the Committee on Welfare Medical Care Programs with the responsibility of investigating the mechanism by which individuals are certified on the aid to the totally disabled program including the criteria for eligibility and the physicians who certify to such eligibility.

Legislative Activity Status report concerning state legislative bills on which the Council had taken a position was presented by Committee on Legislation chairman Dr. Dan Kilroy. Council direction was sought on the following currently pending bills with subsequent action noted: Voted to support S.B. 290 (allowing a person to will any part of his body for transplant purposes); voted to support S.B. 1245 (donation of blood by persons 18 years or older); voted to oppose A.B. 1837 (local school districts entering into contracts with neighborhood health clinics); voted to support S.B. 935 with proper amendments (Advisory Board on Radiation); and voted to oppose A.B. 633 (radiation).

Professional Liability activities were discussed by CMA legal counsel Howard Hassard with details on the current status of the six CMA-sponsored bills pending in the state legislature. Mr. Hassard stressed the importance of the introduction of the bills regardless of their fate this session. He emphasized that gains have been made in drawing the attention of the legislators to this problem area. In another portion of the report, Mr. Hassard suggested that CMA make a thorough study of the entire subject of experimental or investigational procedures in the light of professional liability. Council voted to request the Medical Review and Advisory Committee to study the problem of experimental procedures in consultation with the Judicial Commission and Scientific Board.

Utilization Plan for Hospitals under Medi-Cal was discussed when a joint CMA-CHA proposal was presented regarding a system for more effective utilization of hospital services. This proposal for recommendation to the Office of Health Care Services was approved by Council with amendment to provide for the involvement of California Blue Shield and county society review committees when physicians and other non-institutional providers were involved.

Medical Student Attitudes were approved by Council as the subject of a CMA survey under

the auspices of the Committee on the Role of Medicine in Society. Objectives of the survey as outlined are: (1) to examine the attitudes of students and physicians in California in various phases of education and training to discover how such opinions vary among different groups and (2) to use the data as a base for a follow-up study to be conducted three years hence among the same sample population.

1968-69 Bureau of Research and Planning program objectives were approved with minor amendment on 13 projects presented to Council as follows: (1) California Physician Fee Index; (2) California Blue Shield Usual Charge Index; (3) Continuing Medical Education; (4) Current Medical Practice in Fee Determinations; (5) Group Practice; (6) Cost per Illness and Outcome; (7) Systems Analysis and the Physician's Practice; (8) Consumer Desires and Satisfaction with Health Care Coverage; (9) Socio-Economic Report; (10) Business Aspects of Medical Practice; (11) Medical Expert Panels in Malpractice; (12) Distribution and Characteristics of Hospital Emergency Medical Care Units; and (13) Physician Manpower: Supply and Distribution.

Multiphasic Screening Programs were discussed in a report by Dr. Marvin Shapiro who presented an itinerary for multiphasic screening of cannery workers during the summer and details of last year's multiphasic screening programs. In addition Dr. Shapiro presented several recommendations and the Council voted to approve the following criteria for multiphasic screening programs: (a) that the quality of these programs be upgraded; (b) that careful consideration be given to laboratory facilities in view of quality and cost; and (c) that clinical laboratories working with these programs be involved in a proficiency testing program.

Council also voted to adopt the policy that CMA consider multiphasic screening programs experimental in nature—and further that Council approves CMA's cooperation with organizations offering these programs (when invited) and to urge component medical societies to cooperate, particularly in patient follow-up (after evaluating the specific program and determining the effect of such cooperation).

Rural Health Manpower was the subject of a written and oral report which was based on the CMA Conference on Rural Health Manpower conducted last fall. Specific recommendations as approved by Council were:

- Voted to offer continuing education for rural practitioners in a format that will make it more available and meaningful to them.

- Voted to establish preceptorship programs that will adequately expose health science students to community needs; that include activities that will attract health science candidates from rural areas; that provide adequate faculty in

schools and community; that create involvement in rural community structure; that adequately finance the student and his family.

- Voted to institute a professional education program based on the health team concept and have this concept incorporated in the teaching and training by health science schools.

- Voted to actively involve medical students in the activities of CMA.

- Voted to develop new models for health care coverage and the delivery of health services in rural areas.

Bureau of Emergency Health Services of the State Department of Public Health was recently cut in budget, according to a report presented by Dr. Marvin Shapiro. Dr. Shapiro stated that the activities of this bureau are necessary to meet the provisions of the National Highway Safety Act. Council voted to approve CMA's appealing to the proper state official to effect a contract between the transportation agency and the SDPH, enabling the Bureau of Emergency Health Services to meet the National Highway Safety criteria for: emergency health services activity; driver licensing; and alcohol and driving study. In related actions, Council also approved the following items:

- Voted to request the Committee on Allied Health Personnel to compile a list of schools and courses for training emergency health care personnel in California.

- Voted to accept an invitation to cooperate in a symposium entitled "The Initial Emergency Care and Transportation of the Sick and Injured" to be conducted in September.

1968-69 Commission on Medical Services proposed objectives were approved by Council to include the following proposed projects: (1) Maintenance of Relative Value Studies; (2) Components of Adequate Health Care Coverage; (3) Non-Group Enrollment on a Pooled Basis for the Uninsured Population; (4) Group Practice; (5) Feasibility Proposal for Private, Plus Tax-Incentive System of Health Care for Under-Age 65 Population; (6) Resolution of Diverse Problems Reported to Affect Adversely the Physician's Professional Role in the Care of Patients; and (7) Compilation and Publication of Component Medical Society Grievance Committee Procedures.

Inhalation Therapy

A Joint Statement by the California Medical Association, the California Nurses' Association and the California Hospital Association

INHALATION THERAPY programs are becoming increasingly a part of patient care in hospitals. The organization for delivering such services to patients

in hospitals varies. The administration of such a program in some hospitals is under the department of anesthesiology; in others, the pulmonary department or the nursing service, or other administrative structures. It is recommended the program be under the supervision of a qualified physician of the active medical staff.

Irrespective of the administrative structure, patient safety and sound overall patient care require an understanding, and implementation of the following:

Inhalation therapy is a part of total patient care. The overall supervision and the ultimate responsibility for the patient's plan of medical care is that of the attending physician. Therefore, it is the physician who will prescribe specific inhalation therapy based on the purposes to be accomplished by such treatment. All registered nurses should know inhalation therapy techniques and principles and their relationship to the total nursing care of the patient.

Inhalation therapists, inhalation therapy technicians, registered nurses, and other appropriately prepared personnel may administer inhalation therapy provided:

(a) Those performing inhalation therapy (inhalation therapists, inhalation therapy technicians, registered nurses, or other appropriately prepared personnel) shall be required to demonstrate satisfactorily:

- 1) The ability to operate the necessary equipment, and
- 2) Knowledge of the dosage and effect of any solution or medication used in inhalation therapy.

(b) There is communication and joint planning between the registered nurse responsible for the patient's total nursing care and the inhalation therapist, technician, or other person before, during, and after treatment. This is essential in order to assure safety and the most therapeutic results of overall patient care.

(c) Within each agency there are written policies relative to paragraphs (a) and (b) above and such policies are available to all involved in the patient's care. These policies shall be established jointly by representatives of hospital administration, the medical, nursing, and inhalation therapy staff.

June 15, 1968

❧ In Memoriam ❧

DONALD A. CHARNOCK, M.D.

September 25, 1893-June 16, 1968

LONG A LEADER in the Los Angeles County Medical Association, the California Medical Association and the American Medical Association, Don Charnock was by nature a forceful, strong and outspoken member of the profession. These qualities were tempered by a very fair, honest and judicial mind which made him at once highly respected and successful in whatever he undertook in organized medicine.

During all the time he sat on the Council of the California Medical Association, and particularly during his years of high office as Vice-Speaker, Speaker and President, it was my good fortune to sit on the Council as Editor of CALIFORNIA MEDICINE and to have been associated with him. Our relationship was a close one because, furthermore, we also served as Delegates to the AMA House of Delegates.

Don came to the Vice-Speakership and Speakership of the House of Delegates of the CMA after superb training under the tutelage of his two immediate predecessors, Lowell Goin and Louis Allesen, who were masters of the difficult task of presiding over a large deliberative legislative body—particularly one composed of physicians. As a result he, too, was an outstanding speaker—fair, deliberate, knowledgeable, but always firm and precise in his decisions. The seven years he served as Vice-Speaker and Speaker, 1948 to 1955, revealed qualities of leadership that led to his election to the Presidency of the CMA in 1957.

The high respect in which he was held is indicated by the fact that subsequently he became chairman of the Judicial Commission of the Association and whenever there was a very knotty or difficult problem in medical ethics at the state level, he was the one thought of and turned to by the leadership of the profession. He was recognized as the one outstanding member of the Association who could always be counted on to informally and fairly settle a problem of judicial nature or to preside at a hearing in which problems in judgment of medical ethics were in balance.

Don for years served as a very effective member of the House of Delegates of the AMA. He brought to the delegation the same qualities of leadership and the clear mind he had shown in CMA affairs.

It was my strong hope, along with others, that Don would become a Trustee of the AMA. He would superbly represent the CMA. His capability would have added balance and judgment to the deliberations of the Board. But, when the opportunity was available he, probably wisely, felt he was too old to carry on in so time-consuming and tiring a position.

In his time, then, Don Charnock served the CMA well. He will be a leader long remembered, for he had those elements which naturally result in leadership—loyalty, honesty, fairness and perception, and a capacity clearly to express these qualities by which he lived and carried on whatever he undertook. He was a long-time and true friend of mine and of countless others who, while we mourn his passing, rejoice with me that he lived and that we knew him well.

DWIGHT L. WILBUR, M.D.

BEDRI, MARCEL RECHTMAN, Menlo Park. Died 28 May 1968 in Palo Alto, aged 66. Graduate of the University of Maryland School of Medicine, Baltimore, 1928. Licensed in California in 1963. Doctor Bedri was a member of the Santa Clara County Medical Society.



FINK, DAVID HAROLD, Carmel. Died 21 July 1968 in Carmel, aged 73. Graduate of Detroit College of Medicine and Surgery, 1929. Licensed in California in 1933. Doctor Fink was a retired member of the Monterey County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



FLEWELLING, LOLITA M. R., Napa. Died 25 July 1968 in Napa, aged 72. Graduate of the College of Medical Evangelists, Los Angeles, 1921. Licensed in California in 1921. Doctor Flewelling was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



FRENCH, CHARLES E., San Francisco. Died 17 July 1968 in San Francisco, aged 88. Graduate of the University of Southern California School of Medicine, Los Angeles, 1902. Licensed in California in 1902. Doctor French was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

HAMPTON, STANFORD PAUL, Santa Rosa. Died 14 July 1968, aged 42. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1950. Licensed in California in 1951. Doctor Hampton was a member of the Sonoma County Medical Society.



HAYES, JOSEPH HAROLD, Los Angeles. Died 11 April 1968, aged 52. Graduate of Meharry Medical College, Nashville, 1943. Licensed in California in 1944. Doctor Hayes was a member of the Los Angeles County Medical Association.



HEMINGTON, DAVID EMERSON, Long Beach. Died 21 July 1968 in Long Beach, aged 65. Graduate of Hahnemann Medical College of Philadelphia, 1930. Licensed in California in 1944. Doctor Hemington was a member of the Los Angeles County Medical Association.



HERBERT, WALTER W., San Francisco. Died 18 July 1968 in San Francisco of acute leukemia, aged 44. Graduate of Long Island College of Medicine, 1947. Licensed in California in 1962. Doctor Herbert was a member of the San Francisco Medical Society.



LANE, CAREL W., Eagle Mountain. Died 19 July 1968 in an airplane accident at Eagle Mountain, aged 41. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1956. Licensed in California in 1957. Doctor Lane was a member of the Riverside County Medical Association.



NASH, LOUIS ROGERS, Camarillo. Died 10 July 1968 in Camarillo, aged 61. Graduate of Georgetown University School of Medicine, Washington, D.C., 1933. Licensed in California in 1942. Doctor Nash was an associate member of the Ventura County Medical Society.



NETHERCUT, RUTH ALLEN, Palo Alto. Died 6 August 1968 in San Francisco, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1927. Doctor Nethercut was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



PEYTON, THOMAS ROY, Los Angeles. Died 3 August 1968 in Los Angeles, aged 70. Graduate of Long Island College of Medicine, New York, 1921. Licensed in California in 1944. Doctor Peyton was a member of the Los Angeles County Medical Association.



ROOS, VICTOR OTTO, Redlands. Died 2 July 1968, aged 76. Graduate of the College of Medical Evangelists, Los Angeles, 1935. Licensed in California in 1935. Doctor Roos was a member of the San Bernadino County Medical Society.

SIZEMORE, PLEAS D., Porterville. Died 21 March 1968 of astrocytoma, aged 65. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. M.D. degree from California College of Medicine, 1962. Doctor Sizemore was a member of the Forty First Medical Society.



STERLING, LAWRENCE SHEPHERD, Encino. Died 2 July 1968 in Van Nuys, aged 61. Graduate of Wayne University College of Medicine, Detroit, 1936. Licensed in California in 1946. Doctor Sterling was a member of the Los Angeles County Medical Association.



STRASS, JULIAN J., Inglewood. Died 22 June 1968 in Gardena, aged 60. Graduate of Des Moines Still College of Osteopathy, Des Moines, Iowa, 1951. Licensed in California in 1953. M.D. degree from California College of Medicine, 1962. Doctor Strass was a member of the Los Angeles County Medical Association.



TIBER, LEON J., Los Angeles. Died 20 July 1968 in Los Angeles of cardiac arrest, aged 76. Graduate of the University of Minnesota Medical School, Minneapolis, 1919. Licensed in California in 1930. Dr. Tiber was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



UNCAPHER, REX P., La Jolla. Died 28 July 1968, aged 55. Graduate of Northwestern University Medical School, Chicago, 1938. Licensed in California in 1946. Doctor Uncapher was a member of the San Diego County Medical Society.



WANITA, GEORGE NORMAN, Morro Bay. Died 10 July 1968 in San Luis Obispo, aged 62. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1940. Doctor Wanita was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



WELBOURN, LELAND S., Van Nuys. Died 12 July 1968 in Van Nuys, aged 75. Graduate of the University of Michigan Medical School, Ann Arbor, 1918. Licensed in California in 1919. Doctor Welbourn was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



ZAİK, EDWARD JOSEPH, Los Angeles. Died 28 July 1968 in Glendale, aged 54. Graduate of Wayne University College of Medicine, Detroit, 1938. Licensed in California in 1944. Doctor Zaik was a member of the Los Angeles County Medical Association.



ZUNDELL, JOSEPH LAMONTE, San Francisco. Died 7 July 1968 in San Francisco, aged 62. Graduate of Northwestern University Medical School, Chicago, 1932. Licensed in California in 1949. Doctor Zundell was a member of the San Francisco Medical Society.

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WOMAN'S AUXILIARY

to the California Medical Association

Community Health— A Challenge

A REVIEW OF RECENT medical publications reveals a profusion of articles relating to Comprehensive Health Planning — defining it, interpreting its concepts, stressing its purpose, supporting the format, and lauding its goals.

The intent of medical auxiliaries to pioneer and plan health programs and assist with established ones accords with the objectives set forth in P.L. 89-749. A glance at a list of suggested community health programs would clearly indicate that auxiliaries on national, state, and county levels are vitally concerned with the health needs of our urban and rural areas. Directives from the national headquarters urge study of ways to improve health standards and encourage a diversity of involvement.

Across the nation we are actively participating in screening tests in schools, in immunization programs, in poison prevention, in educational programs on smoking, alcohol, drug abuse, venereal disease, and health frauds and quackery, in disease detection programs, blood banks, mother substitute training programs, pre-retirement counseling, friendly visitor and meals programs, and a host of other activities specifically tailored to provide otherwise unattainable services.

There is, therefore, in the auxiliary a wealth of

experience available to the Health Planning Councils. The legislation permits those who professionally plan as well as those being planned for to share in the responsibility of decision-making. The physician's wife, in the unique role as a consumer married to a provider, is an unusual balance of reactions, and she should not be overlooked as a prospective action-planner. She talks authoritatively, thinks realistically, and is sensitive to the needs which will be considered. Her years of interest and constructive activity in community health problems provide a broad base of understanding, and her awareness of problems outside her geographic region and her access to pertinent information and material can be invaluable.

In California, the County Community Health Chairman and committee members are charged with the careful evaluation of projects and the judicious allocation and distribution of funds. Pilot programs show considerable initiative with emphasis on utilization of "woman-power" as well as money.

In addition to this facet of auxiliary, the physician's wife devotes many hours of service to numerous volunteer agencies. Review of this reservoir of experience suggests that there is an opportunity available for her to serve in an advisory capacity in the entire program of health planning.

On all levels, auxiliary members should be encouraged by the medical profession to participate on planning councils. To this end all members should seek information from the local county medical society on what the Comprehensive Health Planning legislation means and how to become involved in carrying out its provisions.

MRS. BERTRAM H. ECKMANN
Community Health Chairman

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.

Director, State Department of Public Health

The Court's Decision on Alcoholism

IN EARLY 1966 two United States Courts of Appeal handed down decisions holding that a chronic alcoholic may not be convicted for his public intoxication.¹ When this same issue was considered by the United States Supreme Court it was generally anticipated that the Supreme Court's decision would follow that of the lower courts. However, the court ruled in a five to four decision that chronic alcoholism was not a valid defense against a charge of public drunkenness.²

The chief counsel for the defense identified the key to the decision as being based on the court's feeling that there were not enough solid facts to support the disease concept. He went on to say that the physicians' charge for the future is to supply those facts. Much more must be known about what causes alcoholism and how to treat it.

The court decision drew criticism from two American Medical Association officials. Dr. Marvin Block of the AMA Committee on Alcoholism and Drug Abuse recalled that since 1956 organized medicine has defined alcoholism as an "illness that requires and deserves medical treatment."³ He pointed out that alcoholics can be treated by a variety of programs that have proven extremely successful.

Another spokesman, Dr. Dana Farnsworth of Harvard, chairman of the AMA Council on Mental Health, said that careful reading of the court's edicts "foretells an opposite opinion within a few

years."³ He suggests that the tone of the rulings puts physicians on notice that they must work out improved methods for caring for alcoholics now. He identified the need to involve physicians both in private practice and in public health agencies.

While medical officials of the AMA expressed their disappointment in the Supreme Court decision, some of the mass media tended to be critical of the organized medical profession for the "failure" of the Supreme Court to act as had been anticipated. One editorial said that "most physicians will not treat alcoholics and most hospitals do not recognize alcoholism as a certifiable admitting disease."

"The states and local communities" the editorial continued, "are going to have to face the facts realistically that jail is not the answer — and that right treatment will cost money. The programs must be developed. The Supreme Court hinted this is why it did not abolish the drunk tank. There is nothing to replace it. But ordinary decency insists there should be. The AMA should lead the way."⁴

Before the Supreme Court announced its decision the Committee on Alcoholism of the California Medical Association was developing plans for regional training programs on the medical management of acute alcoholism. Now it can be hoped that the CMA will promote a public policy clearly indicating that alcoholism is a major medical problem and not one to be handled by punitive methods.

A leadership role is also required of the California Hospital Association, which is at present in the process of considering a policy statement on alcoholism, similar to that of the American Hospital Association's statement on the admission of alcoholic patients to general hospitals. This policy recommends that the "primary point of at-

tack [on alcoholism] should be through the general hospital. Because of the completeness of its facilities and of its accessibility, it is the logical place where an alcoholic or his family would turn."⁵ It must be recognized, however, that while hospital policy opens the hospital door to patients with alcoholism, the care of individual patients is the responsibility of the attending physician.

This offers a challenge to physicians, both individually and collectively, to guide and assist in

educating the general public that alcoholism is a medical condition requiring treatment by a physician instead of punishment in jail.

REFERENCES

1. Easter vs. District of Columbia, 361 F 2d 50 (D.C. cir. 1966) (en banc); Driver vs. Hermont, 356 F 2d 761 (4th cir. 1966).
2. Powell vs. Texas, U.S. Supreme Court, 17 June 1968.
3. AMA Deplores Rule on Alcoholics, San Francisco Chronicle, 19 June 1968.
4. The Sacramento Bee Editorial Page, 26 June 1968.
5. Statement on the Admission of Alcoholic Patients to the General Hospital—Approved by the American Hospital Association, 29 Sept. to 2 Oct. 1957.

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

The Child Psychiatry Service of the University of Southern California School of Medicine, Department of Psychiatry, is offering three one-year National Institute of Mental Health fellowships in child psychiatry for physicians, beginning 1 July 1969. The stipend is \$10,000 a year. The fellowship is designed to orient the physician to the common emotional problems of children and adolescents and their families. The primary clinical setting is the Childrens Hospital of Los Angeles. Additional orientation and treatment experience will be given at the Los Angeles County-USC Medical Center and the Los Angeles Child Guidance Clinic. For further information or application: Joseph D. Teicher, M.D., USC School of Medicine, Department of Psychiatry, 1934 Hospital Place, Los Angeles 90033.

Granada Hills Community Hospital and The Health Sciences Department of San Fernando Valley State College will hold a two-day symposium on cardio-pulmonary disease, October 12 to 13 on the campus of the college. The program has been approved by the American Academy of General Practice for 16 hours of elective credit for its members.

For registration or information contact Granada Hills Community Hospital, 10445 Balboa Boulevard, Granada Hills 91344.

The second annual Clinical Pulmonary Symposium will be held at Memorial Hospital, Long Beach, 1 November. Further information may be obtained from: Long Beach Tuberculosis and Health Association, 1002 Pacific Avenue, Long Beach 90813.

SACRAMENTO

University of California Extension is sponsoring a training program on Comprehensive Care

of the Cardiac Patient to be held on four successive week-ends in October, in the Auditorium, Mercy Hospital, 4001 J Street, Sacramento. The course is scheduled to begin Saturday and Sunday, October 5 to 6 and end October 26 to 27.

The purpose is to provide sufficient didactic and practical instruction for practicing physicians to become proficient in the care of patients with cardiac disease, including myocardial infarction and other emergencies. The course is planned to give adequate training to potential directors of coronary care units, no matter what their previous training or experience. The fee is \$85.

Further information: University of California Extension, 376 Administration Building, Davis, California 95616 (Attention, Mrs. Nancy Ehrke, programming secretary).

SAN FRANCISCO

The Fourth Annual Clinical Cancer Conference on Advances in the Investigation and Management of Malignant Diseases will be held November 9 and 10 in the auditorium of the Medical Sciences Building, University of California San Francisco Medical Center. It is presented by the Cancer Research Institute, in cooperation with various departments of the University of California School of Medicine, San Francisco, and Continuing Education in Health Sciences, University of California San Francisco Medical Center, and it is co-sponsored by the California Division of the American Cancer Society.

Dr. David A. Wood, director of the Cancer Research Institute, said that the conference has been designed specifically to review and report information concerning advances in the diagnosis and management of certain malignant diseases as encountered in clinical practice by the general practitioner as well as the specialist. It will be presented by authorities in the field of diagnosis and treatment in a wide variety of oncologic problems.

Ten nationally known physicians will be guest speakers at a three-day physicians' postgraduate symposium on heart disease in San Francisco on October 9 to 11. Speakers at the meeting, which is sponsored by the San Francisco Heart Association in cooperation with seven Heart Associations from throughout the San Francisco Bay Area, will be the following physicians:

James K. Alexander, professor of medicine and head of the Cardiology Section, and Denton A.

Cooley, professor of surgery, both of Baylor University College of Medicine, Houston.

Sidney Blumenthal, professor of clinical pediatrics, and John H. Laragh, professor of medicine, both of the College of Physicians and Surgeons, Columbia University, New York.

James W. DuShane, chairman, Section of Pediatrics, and Dwight C. McGoon, chairman, Department of Cardiovascular Surgery, both of the Mayo Clinic, Rochester.

Edward D. Freis, professor of medicine, Georgetown University School of Medicine, Washington, D. C.

Richard Gorlin, director, Cardiovascular Unit, Peter Bent Brigham Hospital, Harvard Medical School, Boston.

Herbert E. Griswold, professor of medicine and head, Division of Cardiovascular-Renal Diseases, University of Oregon Medical School, Portland.

Myron Stein, director, Pulmonary Division, Rhode Island Hospital, Providence.

Physicians from San Francisco and surrounding universities and medical institutions will complete the faculty.

A complete program and registration information may be obtained by calling the San Francisco Heart Association at (415) 982-5753 or writing the organization at 259 Geary Street, San Francisco 94102.

YOLO

Six new appointments to the faculty of the University of California School of Medicine at Davis have been announced by Dean C. John Tupper. Three are to posts in the Department of Pathology and one each in the departments of Pharmacology, Internal Medicine and Human Anatomy.

• Dr. Boris Ruebner, formerly on the faculty at Johns Hopkins, has been named professor of pathology; Dr. Larry W. McDonald, a research associate at the University of California, Berkeley, and a research physician at Lawrence Radiation Laboratory, has been appointed an assistant professor; and Dr. Joseph L. Theocheung of Surabaya, Indonesia, will be an instructor in pathology.

• Dr. Keith F. Killam, Jr., professor of pharmacology at Stanford University School of Medicine, will become chairman of the Department of Pharmacology at Davis.

• Dr. Carroll E. Cross has been named assistant professor in the Department of Internal Medicine.

Most recently an instructor in medicine at the University of Pittsburgh, Dr. Cross will continue research in pulmonary disease at Davis.

• Dr. Alexander Barry was appointed professor of human anatomy and associate dean of student affairs. Dr. Barry has been a professor at the University of Michigan since 1946 and recently served as associate dean there.

GENERAL

A medical advisory committee representing 11 northwestern California counties has been named to assist Regional Medical Programs (Area I) in establishing community health projects relating to heart disease, cancer and stroke. Dr. Elliot Rapaport, acting coordinator of the Area I RMP agency which serves much of the Bay Area and the coastal counties north to the Oregon border, said that the group will act as a final review body for regional medical proposals before they are submitted to the California Committee on Regional Medical Programs for possible funding from the national RMP office in Bethesda, Md.

The committee appointments, made by Stuart Cullen, M.D., dean of the University of California, San Francisco, School of Medicine, which is the home base center for RMP Area I, include representatives from the community at large and from the five district advisory groups regularly working with the RMP health planning staff to devise projects to meet local community needs.

Serving on the new Area Advisory Committee from the Alameda-Contra Costa District Advisory Committee are Frederick Ackerman, M.D., William Donald, M.D., and Frances James, R.N.

K. E. Mooslin, M.D., chairman of the Humboldt-Del Norte District Advisory Committee, and his fellow committee member, H. E. Waite, president of the North Coast Health Facilities Planning Association, represent that two-county area. Norman Carrigg, M.D., chairman of the Marin District Advisory Committee serves with Judge Alvin Goldstein of that committee. The Redwood Empire District Advisory Committee for RMP will be represented on the new Area Advisory Board by Norman Panting, M.D., and W. H. Schneider, administrator of the Sonoma Valley District Hospital.

Representatives from the San Francisco Advisory Committee include David McDaniel, an official of U.S. Steel Corp.; Victor Richards, M.D., and Malcolm McIlroy, M.D.

Representatives at large are **Terrine Adler**, M.D., University of California School of Medicine; **Bradford Lundborg**, M.D., of Santa Rosa, member of the Redwood Empire District Advisory Committee for RMP; **Robert Mason**, administrator of Peralta Hospital in Oakland; **Donald MacDonald**, M.D., of Vallejo, president of the Redwood Empire Heart Association; **Alberta Parker**, M.D., of the School of Public Health, Berkeley; **Irene Pope**, R.N., director of nursing services at San Francisco General Hospital; **Benson Roe**, M.D., of the University of California School of Medicine, and **Byron Rumford** of the California Health and Manpower Council.

INFORMATION

Coronary Care Unit

Personnel Training

FUNDS IN EXCESS of \$350,000 for coronary care unit training programs have been allocated to the University of Southern California's School of Medicine by the California Committee on Regional Medical Programs for heart disease, cancer and stroke, according to a recent announcement by the state committee.

Dr. Donald W. Petit, USC clinical professor of medicine and director of the Area V Regional Medical Program, described the activities that will be initiated under the operational grant as the beginning of a comprehensive training program for physicians and nurses in techniques of coronary care.

Initially, training will be conducted at the Los Angeles County-USC Medical Center, which will be the central training point, and at Good Samaritan and St. Vincent's Hospitals. Selection of these hospitals by the Area V Cardiac Committee under the chairmanship of Dr. George C. Griffith, emeritus professor of medicine, was based on the existence of operational programs at each institution that are ready to be expanded, and on their central location. Dr. Petit said that there will be additional community hospitals involved in the training program within a year, according to a planned expansion of the project.

Committee co-chairman Dr. Milford G. Wyman, USC associate clinical professor of medicine who will be responsible for the overall training program, said the nucleus of the coordinated coronary care plan for the community will be those physicians who are trained as unit directors.

"Hospitals will be asked to select the one or two doctors on their staff who will be responsible for their respective coronary care units," Dr. Wyman explained. "These physician-directors will be given an intensive two-week course at one of the training hospitals in the techniques necessary for the operation of coronary care units. Training will include laboratory instruction in such procedures as arterial puncture, pacemaker placement, the detection and management of arrhythmias, and treatment of shock and congestive failure."

Dr. Wyman said the program will be structured so that it can also provide continuing education for another category of physicians. "This second, larger group will include physicians who care for patients with heart attack," he said. Group II would not require the training in setting up and operating coronary care units, but would be given a refresher course in the anatomy and physiology of the heart in normal and disease states, and instruction in the diagnosis and treatment of acute coronary disorders.

At the County-USC Medical Center and at the other two hospitals selected for initial training programs, nurses from hospitals in Area V will undergo a four-week instruction program in the specific understanding of the circulatory system, heart disease, and the complications associated with the disease and their implications in nursing care. The program will also train nurses in the use of special monitoring devices and electrical equipment utilized in coronary care units. Care of patients in the unit will be part of the training and will stress such things as observation of the patient's physical and emotional responses to illness.

Dr. Wyman said trainees for the four-week program will be accepted from hospitals that already have coronary care units established or ready to function, and from facilities that are planning such units, in that order of preference.

"One of the important criteria for the selection of nurses for the training program is whether they will be returning to a coronary care unit that has a trained physician-director," Dr. Wyman said. "This assures the unit a good working team." Dr. Wyman added that experience has shown that

nurses returning to hospitals without a physician-director of the unit quickly lose their skills.

In both the physicians' and nurses' training program, the concept is that those trained under the guidance of the Regional Medical Program will thereafter train others at their individual hospitals. "Our objective in the nurse training program is to develop informed, competent and highly skilled nurses who will assume a leadership role in planning, administering, and evaluating the nursing care of patients in coronary care units in the community," the USC cardiologist said.

The training programs will be supervised by the head of the cardiology division at the USC School

of Medicine, assisted by the directors of the coronary care unit and the arrhythmia control team at the County-USC Medical Center. They will be assisted by a staff of highly-trained specialists in cardiovascular diseases.

Dr. Petit said that one of the first steps to be undertaken under the grant will be to participate in the planned enlargement of the coronary care unit at the County-USC Medical Center from its present four-bed capacity to 16 beds. "The groundwork for an effective, on-going training program has already been established at this unit, which has been in operation since 1966," Dr. Petit said.



The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 64 of the Advertising Section.

AN ATLAS OF SURGERY OF THE FACE, MOUTH, AND NECK—Robin M. Rankow, D.D.S., M.D., Assistant Clinical Professor of Anatomy, College of Physicians and Surgeons, Columbia University, and Assistant Attending Surgeon (Head and Neck), Presbyterian Hospital, New York City; Attending Surgeon (Head and Neck), Knickerbocker Hospital, New York City; Attending Surgeon (Chairman, Division Head and Neck Surgery), Bronx Lebanon Hospital Center, New York City. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 292 pages, \$25.00.

This Atlas is a useful supplement to the *Atlas of Head and Neck Surgery* by Loré, also published by Saunders. It uses the same concise but clear arrangement as Loré did with the steps of the surgical procedure on one page and drawings illustrating the steps on the opposite page. The material covered includes fractures of the mandible and facial bones, removal and subsequent reconstruction of lesions on the lips and face, the jaws and palate, and floor of the mouth and tongue. The book also includes operations on the temporomandibular joint, the radical neck dissection, removal of congenital cysts of the neck, surgical repair of malformations of the jaw, and salivary gland surgery. The strength of this book is its emphasis on applied anatomy and the orderly way in which the sequence of the surgical steps is established with drawings and written descriptions. In my opinion its major weakness is that although it describes itself as covering the neck, it does not include larynx and pharynx surgery.

HERBERT H. DEDO, M.D.

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THE MANAGEMENT OF TRAUMA—By members of the staff of The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital—Edited by Walter F. Ballinger, II, M.D., formerly Associate Professor of Surgery, The Johns Hopkins University School of Medicine, Baltimore; Bixby Professor and Chairman, Department of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes Hospital, St. Louis; Robert B. Rutherford, M.D., Assistant Professor of Surgery, The Johns Hopkins University School of Medicine; Surgeon-in-Charge, Emergency Service, The Johns Hopkins Hospital; and George D. Zuidema, M.D., Professor and Director, Department of Surgery, The Johns Hopkins University School of Medicine; Surgeon-in-Chief, The Johns Hopkins Hospital. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 815 pages, \$25.00.

Management of Trauma is timely and up to date: injuries from auto accidents and rioting are increasing; trauma is the leading cause of death among persons between the ages of one and thirty-seven; and life-saving and disability-minimizing procedures continue to be improved.

The book is comprehensive but concise and logically organized. The first chapter on "Initial Evaluation and Treatment of the Injured Patient" starts off with this statement: "The first aim of the physician examining an injured person is the preservation of life." The reader is

then taken through the various steps to be taken in appropriate sequence. The recognition and diagnosis and the initial treatment and definitive management of every type of injury to every part of the body in all age groups are adequately covered as one proceeds through the 23 chapters. To indicate the thoroughness and thoughtfulness of the authors, the final five chapters are entitled: Trauma and the Child; Radiation Injury; The Role of the Internists in Trauma; Acute Trauma from a Psychological Viewpoint; and Mass Casualty Management.

The text is easy to read and is adequately illustrated with pictures, diagrams, and charts. The book should appropriately find its place in every medical school and hospital library and in every first-aid and emergency room where the English language is read. It should serve equally the student learning the pathophysiology of trauma and the principles of its management and the experienced first-contact (family) physician and the consulting surgeon who frequently need a reference book to review some aspect of this subject.

LELAND B. BLANCHARD, M.D.

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ESSENTIALS OF BLOOD GROUPING AND CLINICAL APPLICATIONS—K. S. Ranganathan, M.R.C.S., L.R.C.P., Consultant, Blood Bank, The Voluntary Health Services Medical Centre, Madras; Formerly Officer on Special Duty (Blood Transfusion), Directorate-General of Indian Medical Service, New Delhi. Grune & Stratton, Inc., Publisher, 381 Park Avenue South, New York, N.Y. (10016), 1968. 178 pages, \$6.00.

This small volume presents the most recent account of blood grouping and its applications in a form which is suitable for the requirements of technologists and relatively inexperienced physicians. It is directed at an audience whose needs are met by only one other publication: *Technical Methods and Procedures of the American Association of Blood Banks*.

In general, the recommended serologic procedures in the two publications are identical. Ranganathan's book covers a more limited area and provides more detailed explanations. It is particularly good on interpretation of reactions, on precautions to be observed and on comparing the relative usefulness of procedures directed at the same goal.

Statistics for the frequency of occurrence of various blood types are given for the country of India, and are thus not useful in this country. The author has sided with Alexander Wiener in the latter's campaign to restrict Rh nomenclature to the Wiener terminology.

Several minor points deserve comment. The author continues to use "univalent" as one synonym for an incomplete antibody, although evidence is now clear that such antibodies are truly bivalent. He states that purified A and

B substances may be added to group O blood given to a non-O recipient without risk of immunization, whereas such a procedure can result in development of high titer immune anti-A and/or anti-B. He states that O is a true agglutinin, although admitting later that the O gene is an amorph (without any detectable end-product). Finally, and most important, he says that it is not realistic or practical to do the antiglobulin compatibility test routinely. Experts in this country feel that the antiglobulin phase is mandatory.

This is a well-written book, and those who wish to read an introductory text on blood grouping will find it quite useful.

HERBERT A. PERKINS, M.D.

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HEREDITARY DISORDERS OF ERYTHROCYTE METABOLISM—Proceedings of the Symposium held February 13 to 15, 1967, at the City of Hope Medical Center, Duarte, California; City of Hope Symposium Series: Vol. I—Edited by Ernest Beutler, M.D., Director, Hematology Department, Chairman, Division of Medicine, City of Hope Medical Center, Duarte, California; and Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California. Publication of this volume was supported by a grant from the Institute for Advanced Learning in the Medical Sciences of the City of Hope. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 343 pages, \$9.00.

An excellent text for the expert or serious student of genetic disorders or enzymology, this is hardly a volume for the casual reader. The orientation is toward genetics, enzymology, and red cell metabolism in about that order. The clinical manifestations and management of the hereditary red cell disorders are mentioned occasionally. The book is based on a symposium held at City of Hope Medical Center in February, 1967, and is consequently quite up to date in a field which is changing only moderately rapidly. The list of participants in the discussions includes internationally known scientists as well as relative unknowns. All the chapters are by acknowledged experts in their fields. Particularly well written are the chapters by Huennekens on "Methemoglobin Reductases," Jandl on "Hereditary Spherocytosis," and Valentine on "Hexokinase and Hemolytic Anemia." The final chapter by Arno Motulsky on "Contributions of Hereditary Disorders of Red Cell Metabolism to Human Genetics" bears the usual hallmarks of this author; it is lucid, wide ranging, and stimulating. Beutler has done an extremely competent job of editing. Thanks to his efforts, the discussions occurring at the end of each chapter supply additional detail and extend the formal presentations. I suspect that for the next two or three years this will be the standard reference work in this field. Hopefully at the end of that time Dr. Beutler will organize another symposium.

MARTIN J. CLINE, M.D.

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NEW DRUGS—1967—Evaluated by the AMA Council on Drugs. American Medical Association, 535 North Dearborn Street, Chicago, Ill. (60610), 1967. 590 pages, \$3.50 (\$1.75 for medical students, interns and residents).

New Drugs, a publication of the Council on Drugs of the American Medical Association, is a deeply buried gold mine which the physician may not find unless he prospects carefully indeed. It is an unpretentious blue paperback and has all too little in its advertising or its publicity to point to its value. However, it has been planned to meet the specific needs of practicing physicians for up-to-date, authoritative and unbiased information on the more recently introduced drugs. Doctors can save themselves a good deal of time and trouble by reading or consulting this book instead of the literature of the manufacturer.

The chapters and sections are based insofar as possible on therapeutic classifications. Each chapter or major section of it contains an introductory statement that briefly discusses the relationships of the newer drugs to each other and the older drugs. All drugs discussed in the text are indexed by their nonproprietary and trade names; therapeutic uses and classifications are also included in the index. In addition, a separate listing of Canadian trade names is given, as well as the names and addresses of the pharmaceutical firms involved.

Some drugs are discussed in detail in monographs. These are individual agents generally available in the United States and introduced within the past ten years. The statements on each are based on the evaluation of the available laboratory and clinical evidence by the Council of Drugs and its consultants. The 1967 edition contains much new material and considerable revision of monographs and introductory sections from the 1966 edition.

This book presents a concise, unbiased assessment of the newer drugs. It is recommended for the physician's reference shelf.

EDGAR WAYBURN, M.D.

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ATLAS OF STRABISMUS—Gunter K. von Noorden, M.D., Associate Professor of Ophthalmology, and A. Edward Maumenee, M.D., Professor of Ophthalmology, The Wilmer Institute of Ophthalmology, The Johns Hopkins University, School of Medicine, and Hospital, Baltimore, Maryland. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1967. 188 pages, 115 illustrations, 29 in color, by Robert B. Wingate, M.S., F.R.S.A., \$17.50.

The *Atlas of Strabismus* by Gunter von Noorden and A. E. Maumenee is really more than an atlas. It is a copiously illustrated textbook devoted to the sub-specialty of strabismus practice. It covers the definitions of terms used in this type of work; it illustrates the essentials of clinical testing procedures; and it summarizes very concisely the various syndromes that one is likely to encounter in patients with a disturbance of eye movements.

Clearly, the book is written not only for ophthalmologists, but for pediatricians, neurologists, and general practitioners as well. The approach is, by and large, extremely simple; and no previous knowledge of the field is necessary to grasp the concepts put forth by the authors.

Robert Wingate's illustrations, which, for the most part, consist of simple line drawings, are admirably clear. They bring out the points which the authors wish to make with graphic simplicity and eliminate distracting side-issues. Color is used sparingly and only for emphasis in certain of the drawings. The clinical photographs used for the demonstration of specific defects in certain types of patients are well chosen and of excellent quality.

The text is physiologically sound; and in those theoretical areas of strabismus practice, such as the sensory aspects of oculomotor anomalies, where there is considerable latitude of opinion, no attempt is made to convert the reader to one school or another. The objective findings are presented, and the reader is left on his own to choose the mode of treatment which might be most appropriate for his patient. Treatment is not emphasized in this book; and relatively little is said about surgical techniques, which are, perhaps, better illustrated in other texts.

As an ophthalmologist who is concerned relatively little with problems of strabismus in his own practice, I find the book extremely useful as a form of refresher course. I recommend it highly as a useful addition to the library of the ophthalmologist, neurologist, and pediatrician.

G. RICHARD O'CONNOR, M.D.

DYSLEXIA—DIAGNOSIS AND TREATMENT OF READING DISORDERS—Edited by Arthur H. Keeney, M.D., D.Sc., Professor and Chairman, Department of Ophthalmology, Temple University School of Medicine; Ophthalmologist-in-Chief, Wills Eye Hospital, Philadelphia, Pennsylvania; and Virginia T. Keeney, M.D., Project Coordinator, National Conference on Dyslexia, Philadelphia, Pennsylvania. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1968. 182 pages, \$12.00.

This book is the product of a National Conference on Dyslexia, sponsored by the American Committee on Optics and Visual Physiology and the U.S.P.H.S. Neurological and Sensory Disease Service Program. The conference brought together fourteen distinguished participants to consider the controversial and often confusing topic of Dyslexia. The contents of the book, following the proceedings of the conference, are organized into four major sections, with verbatim reports of discussion following each section. Topics include definition, diagnosis, correlated functions and disturbances, etiology, historical considerations, remediation, and research needs.

The volume might well be titled "A Search for Identity." Definitional problems and confusions clearly point up some major theoretical issues of practical import. Is Dyslexia a specific, unique syndrome, or does the term merely define the most extreme end of the reading distribution? That is, are we dealing with qualitative as well as quantitative difference among poor readers? Participants were not always in agreement regarding this question. Difficulties of identification and diagnosis were apparent from the clinical descriptions presented. All participants agreed that dyslexics evidenced prolonged and severe reading retardation; there was less agreement as to consistency of behavioral and/or neurological and physical correlates. Consensus as to the need for early and accurate diagnosis was somewhat mitigated by the lack of agreement as to precise definitional or diagnostic criteria, whether appearing early or late in the developmental history. There was, for example, marked disagreement as to the diagnostic significance of motor clumsiness, and question as to the meaning of information pertaining to genetic characteristics. Participants were split on the question of appropriate remediation, ranging from support of programs strongly based in educational techniques to management programs utilizing medication, eye training, and motor coordination training. The majority of participants had strong doubts as to the efficacy of some popular motor training or patterning programs, although there was disagreement as to the importance of motor coordination training as it relates to Dyslexia.

In a volume of this kind in which all participants made thoughtful contributions, it is difficult to single out particular papers. However, the practicing physician will likely find the papers by Rabinovitch, DeHirsch, Critchley, and Goldberg of particular interest as they provide information of clinical relevance. Suggestions by Botel, Orton, Nicholl, Cruickshank, and Benton as to remedial and therapeutic practices provide the reader with some ideas as to the scope of remedial practices; none presents definitive evidence, but in total they provide a range in points of view. Critchley's final chapter points up the complexities of the subject by defining topics "worthy of research."

A major value of this book is that it may alert the practicing physician to the problems of the child with severe reading disturbance; it has limited theoretical or research significance; its real merit is in the clinical implications. Sensitivity to the problem of Dyslexia may be a major step in coping with the problem. In the foreword to the book Burian described Dyslexia as a subject "in flux" with "uncertain parameters." The reviewer heartily agrees

with this description. The reader will find the book a stimulating and provocative introduction into a fascinating and complex topic.

BARBARA KEOGH, Ph.D.

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HEREDITY, DISEASE, AND MAN—Genetics in Medicine—Alan E. H. Emery, M.D., M.Sc., Ph.D., M.R.C.P.E. University of California Press, Berkeley, California (94720), 1968. 247 pages, \$6.95.

As the perusal of any daily newspaper will indicate, medical genetics is indeed a topic of immense interest to the general public. It is, therefore, rather timely for this review by Dr. Alan E. H. Emery of *Heredity, Disease, and Man: Genetics in Medicine*. As is stated in the author's preface, the book is written primarily for "high school and college graduates majoring in various scientific fields." Physicians need not be excluded, however, since it does represent an excellent review of a rather broad area of medicine in which advances in knowledge often exceed the ability for thorough comprehension by most physicians. Many of the signal experiments in our understanding of genetic diseases are outlined with clarity, with ample reference to common hereditary diseases rather than those obscure maladies so commonly used as examples in texts of this sort. For the reader unfamiliar with medical jargon, an excellent glossary is provided. Although appropriate for most readers, the bibliography is incomplete for the serious student of genetics. The rather complete index is a welcome addition, too often overlooked in texts designed primarily for non-medical readers.

The contents of a book of this type are always open to some criticism. A chapter on treatment of genetic diseases would be useful, particularly to the layman unfamiliar with research in this area. The relationship of genetics to organ transplantation is of such vital interest and importance in this decade as to warrant more thorough discussion. Increased use of pictorial and graphic material would improve some of the chapters and inclusion of photographs in place of some of the less sophisticated diagrams would give more impact to some of the important theories.

Two chapters deserve particular merit; those entitled "Chromosomes and Chromosomal Abnormalities" and "Genetics and the Physician." The former is an exceptionally thorough review of this rapidly growing field and the latter, a helpful discussion of genetic counseling and its problems.

This book represents the second in a series entitled *Perspectives in Medicine*, edited by Leo van der Reis, M.D., which is designed to bridge the gap between technical scientific knowledge and the practical understanding of it by interested medical and non-medical personnel. Professor Emery's review holds true to this charge.

HIBBARD E. WILLIAMS, M.D.

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NEURORADIOLOGY WORKSHOP—Volume III: Non-Neoplastic Intracranial Lesions—Leo M. Davidoff, M.D., Professor and Chairman Emeritus, Department of Neurosurgery, Albert Einstein College of Medicine, Bronx, New York; Consultant in Neurosurgery, Montefiore Hospital and Medical Center, Bronx, New York; Harold G. Jacobson, M.D., Chief, Division of Diagnostic Radiology, Montefiore Hospital and Medical Center, Bronx, New York; Professor of Radiology, Albert Einstein College of Medicine, Bronx, New York; and Harry M. Zimmerman, M.D., Chief of Laboratory Division, Montefiore Hospital and Medical Center, Bronx, New York; Professor of Pathology, Albert Einstein College of Medicine, Bronx, New York. Grune & Stratton, Inc. 381 Park Avenue South, New York, N.Y. (10016), 1968. 577 pages, \$34.75.

This text is the third volume of a four volume Neuro-

radiology Workshop series. It was preceded by *Volume I: Scalp, Skull and Meninges*, and by *Volume II: Intracranial Tumors Other Than Meningiomas*. The final volume, *Volume IV: Diseases of the Spine*, is to follow.

Volume III, like the preceding volumes, primarily is based on the transcribed and edited tape recorded proceedings of the weekly combined conferences of the Departments of Radiology, Neurosurgery, Neurology, and Neuropathology of the Montefiore Hospital and Medical Center.

The subject matter is presented as case histories in the clinico-pathological conference format with the cases grouped in six categories: Congenital Anomalies, Trauma, Infection, Vascular Anomalies, Degenerative Diseases, and Diseases of Unknown Etiology. With a few exceptions, the subject matter is restricted to cases from the Montefiore Hospital and Medical Center. As a result, some clinical syndromes are not included. Although it is not an all inconclusive review of the entire neuroradiology field, it does cover the more important aspects with good clinical and neuropathological correlation.

Also included in the discussion of some cases are the indications and contraindications for some of the diagnostic and surgical procedures and therapeutic approaches. It must be recognized by the reader that the views expressed represent opinions and experiences of the authors, all recognized authorities in their respective fields, but are not necessarily always in agreement with other authorities. Of course, this is to be expected and, in fact, makes the book more interesting.

Newer diagnostic aids, such as radioisotope scans, echoencephalography, and subtraction techniques were not included, since most of the cases were seen and recorded at a time when these newer diagnostic aids were still in the early development stage and had not been adequately evaluated.

All cases have accompanying pertinent radiographic reproductions and many also have gross and microscopic pathological illustrations. Although some of the radiographic reproductions are of excellent quality, many are only fair and some are rather poor. At least a moderate degree of prior neuroradiographic knowledge is required for the reader to appreciate many of these illustrations. The bibliography is quite limited, and the index only fair. These deficiencies are inherent in the organizational format, of course.

This is an interesting, informative book, pleasant reading, and is recommended for anyone interested in neuroradiology. However, because of the organization (case history-CPC format), anyone desiring a primary quick reference source for a specific question might be frustrated or disappointed.

CALVIN RUMBAUGH, M.D.

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(MAJOR'S) PHYSICAL DIAGNOSIS — SEVENTH EDITION — Edited by Mahlon H. Delp, M.D., Peter T. Bohan Professor of Medicine, The University of Kansas School of Medicine, Kansas City, Kansas; and Robert T. Manning, M.D., Associate Professor of Medicine, The University of Kansas School of Medicine, Kansas City, Kansas. 356 pages, \$9.50.

This is a thoroughly revised new edition of a well-known textbook. It is generously illustrated with black

and white photographs, diagrams and phonocardiographic tracings. Chapters have been contributed by 16 specialist authors. They have been edited to a uniformly clear and concise style and each is followed by a good list of references. Distinctive are the chapter by Ralph Major on the history of physical diagnosis and one by Robert Manning on theoretical aspects of making a diagnosis.

Like all textbooks of physical diagnosis, this is only a primer, designed to help the beginner but, aside from the references, of little use to practitioners or advanced students. Much attention is given to physical manifestations and very little to history taking, analysis of symptoms or how to record the data. Not enough emphasis is placed on the pathophysiological basis of symptoms and signs. This reviewer thinks today's second-year student of clinical medicine deserves a considerably more sophisticated (but still not encyclopedic) introductory textbook. None exists.

ELLEN BROWN, M.D.

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SURGERY OF THE AGED AND DEBILITATED PATIENT— Edited by John H. Powers, M.D., Surgeon-in-Chief Emeritus, The Mary Imogene Basset Hospital, Cooperstown, New York. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 611 pages, \$19.50.

This book's 18 chapters deal with every aspect of surgery of the aged patient and was written by outstanding national authorities. The problems of the aged are presented from the viewpoint of the physiologist, biochemist, internist, surgeon, anesthetist, and psychiatrist on the methods of investigation and preparation of the aged or debilitated patient for surgery, and emphasizes the co-existence of physiologic as well as degenerative entities. The authors do not present the details of operative procedures, but rather emphasize those particular points, so that the elderly patient may adjust to the vicissitudes of surgery in order to manage not only senescent changes but also associated diseases. The chapters on the Physiology of Aging, the Pathogenesis of Diseases of Senescence, and the Metabolic Management of Elderly Surgical Patients present important basic knowledge, often overlooked, with which the surgeon should be familiar. The differentiation between biologic and pathologic aging permits one to recognize the decrements of functional capacity of organs and systems associated with aging and those due to disease processes. The aged and debilitated patient is discussed from the standpoint of the changes in body composition, chemistry, metabolism, blood volume, infections, water and electrolyte requirements, nutrition, cardiac, and the reserves of other systems. The discussion of the preparation of the aged or debilitated patient undergoing elective surgery is excellently presented and if followed will afford improved results. The preparation and timing for emergency surgery is also emphasized. Those particular features or differences in conducting the operative procedure are emphasized.

This volume incorporates pertinent features of anesthesia, vascular surgery, fractures, cancer, hepatic function, trauma, and sources of mortality in the aged patient. It will be of great benefit both to the surgical resident staff and the surgical practitioner.

LEON GOLDMAN, M.D.



A Screening Project for the Geriatric Mentally Ill

Appraisals to Determine Suitable Care Facilities

RUSSEL F. RYPINS, M.D., AND MARY LOU CLARK, ACSW, *San Francisco*

■ *The Geriatric Screening Project, the purpose of which is to determine whether referred patients can be dealt with by some means of care less drastic than commitment to a state hospital, has significantly reduced commitments from San Francisco. Geriatric commitments previously numbered almost 500 a year. In its first three calendar years, 1,290 persons were directly served by the project. The commitments dropped successively in the three years to 40, to 12 and then to three.*

The project has demonstrated that vast reductions of geriatric commitments can be achieved with enlightened screening and recommendations before resort to petition for mental illness is considered. Essential to the dramatic success are home visits, supportive community resources and a dedicated staff unafraid to meet the depressing needs of old people.

In March, 1963, Mrs. X, aged 90 years, was arrested on a Superior Court-approved Petition for Mental Illness. Her history was of a recent fall in a dizzy spell, followed by inability to walk or talk. There had been some mental deterioration associated with confusion. She had a five-day routine "period of observation" on the psychiatric wards of the San Francisco General Hospital; she

was then committed to a state hospital, almost routinely, away from family and friends, on a diagnosis of chronic brain syndrome with cerebral vascular accident. The five-day "period of observation" intensified her emotional disturbance and increased her agitation.¹ This, of course, facilitated the court's prerogative to order commitment. But *in the light of patient-needs her commitment was inappropriate.*

THE FOREGOING IS A true case. Mrs. X is, or was, a living, sensitive, suffering person. She was neither dangerous nor even harmful. But she was sick with

¹ Geriatric Screening Project, California Department of Mental Hygiene.

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Reprint requests to: State Department of Mental Hygiene, Geriatrics Screening Project, 800 Potrero Avenue, San Francisco 94110 (Dr. Rypins).

an organic brain disease and a resultant brain dysfunction or "decompensation" with emotional disturbances. Such brain decompensation or delirium is frequently seen in older persons with chronic brain disease, and very frequently leads to inappropriate commitments. Cognizant of this, the state legislature authorized extensive studies concerning geriatric commitments. And in 1963 funds were appropriated by the legislature for a pilot Geriatric Screening Project (GSP) which, it was hoped, might prevent some of the wrong geriatric commitments. Arbitrarily the 65th birthday was decided upon as the start of the geriatric age by the project.

The case of Mrs. X was typical of the psychiatric procedure in San Francisco County up to 1 July 1964. On that date the Geriatric Screening Project tentatively tried a pioneer program of pre-petition screening of persons over 65 years of age, threatened with Petition for Mental Illness. This was aimed at deciding which disturbed geriatric persons should be "screened-in" to the psychiatric wards for further evaluation and possible commitment. But equally important was to "screen-out" those persons not needing petition, or even psychiatric hospitalization^{2,3,4}; and, for the latter, to assist in the development of appropriate and adequate and humane arrangements individualized to each patient. At the end of two months of trial, this pre-petition screening proved so valuable to all concerned that it became the permanent focus of the Geriatric Screening Project.⁵ It also has become a proposed standard for all counties relative to proposed petitioning regardless of age, and has become established procedure in several California counties.⁶

Historically, state mental hospitals have been used almost indiscriminately and almost routinely for "warehousing" disturbed elderly persons.⁷ This traditional practice is undergoing a change. The change reflects a trend away from using state hospitals as providers of custodial care.⁸ The change also reflects a newly developing concern for more effective therapy for disturbed persons of all ages, including the aged.^{9, 10}

In addition, "It had long been accepted that early diagnosis and prompt treatment at the local level could, and should, act as a prodigious force to interrupt progression of mental illness and thus eliminate the need for state hospitalization."¹¹ Furthermore, humanitarian concern for patients as persons, including our elderly patients, revolts

against having them suddenly uprooted and transplanted into a state hospital environment. This is seriously traumatic to many of them and is earnestly to be avoided.

As of 1961, there were over 11,000 geriatric in-patients, like our Mrs. X, in our California state hospitals. In nearly half of them (47.5 percent) the diagnosis was related to senility or organic brain disease, (excluding those associated with alcoholism).¹²

DeWitt State Hospital, in a special study, reported that, excepting a few cases, approximately 50 percent of these elderly patients "could be adequately cared for in other than a state hospital."¹³ In general, "... the majority of these [geriatric] patients did not need, nor would they benefit from, further care in a state mental hospital."^{14,15,16,17}

In addition the Code "*prohibits* the commitment of chronic, harmless, mentally unsound persons to state hospitals . . . The cooperation of those concerned [is solicited] in order that the case of every older person will be thoroughly reviewed with the object of finding the best plan for that person before consideration is given to commitment to a state hospital."^{18,19}

A substantial percent of the committed geriatric group had needs primarily for change in living situations, for supervision, and for treatment, both systemic and psychiatric. Their commitment was therefore considered to be inappropriate commitment of older persons who were disturbed, as a result of organic brain disease, but harmless.

Pathology and Symptoms

Organic brain disease of the senium is mostly secondary to cerebral arteriosclerosis or to senile brain disease. Less frequent causes are chronic and acute alcoholism, metastatic or primary malignant lesions and Addisonian anemia, among many others. When the pathologic changes are irreversible it is called chronic brain disease (CBD), and the resultant clinical manifestations are called chronic brain syndrome (CBS).

Persons with CBD are readily subject to additional and reversible brain changes when under stress. Medical examples of such stress are pneumonia, bronchitis, upper respiratory infection, malnutrition both quantitative and qualitative, anemia, cardiac decompensation, diabetes and fresh "strokes," among countless others. Social stresses sometimes precipitating reversible changes include loneliness, economic difficulties and forced retire-

TABLE 1.—*Geriatric Admission Rates to State Hospitals per 1,000 county population aged 65 and over*

	1962	1963	1964	1967
State total	1.9	1.8	1.6	0.96
Los Angeles	0.5	0.7	0.5	0.43
San Francisco	5.1	5.0	4.9	0.39*
S.F.:L.A. ratio	10x	7x	10x	ca 0.9x
S.F.:State total	2.7x	2.8x	3.1x	ca 0.4x

ment from employment. Any of these can underlie disturbed conduct which is reversible on removal of the specific underlying stress. Deviant conduct presumed to be—or which already has shown itself to be—reversible, in the psychiatric literature is called acute brain syndrome (ABS)^{20,21,22} regardless of abruptness or slowness of onset and regardless of duration. It is to be noted that older brains give rise to ABS from much slighter stress than is required for ABS in younger brains. But most important, a rational treatment program is possible.²³ Appropriate treatment of the patient in the local community frequently can make commitment for ABS unnecessary.

Objectives

Because the high rate of geriatric commitments was recognized as a serious concern, the 1963 legislature provided special funds to set up a study project concerning them. Over the years San Francisco had one of the highest county geriatric commitment rates in California²⁴ (Table 1), so San Francisco County was chosen for this study.* Over the preceding years the average number of geriatric commitments from this county was almost 500 a year.

The primary objectives of the program were:

1. To seek out any existing community resources and services which possibly could meet the needs of mentally disturbed older persons better than they are met by commitment to state hospitals.
2. Should this seeking out uncover such resources in the community, to use them in an effort to reduce the number of inappropriate commit-

*The Bureau of Social Work of the Department of Mental Hygiene was delegated responsibility for developing the project, and it selected San Francisco. It was agreed that the unit would operate in cooperation with the San Francisco County Community Mental Health Services.

*This rate of 0.39 truly should be much lower. There were 36 geriatric admissions to the state hospitals from San Francisco. But this included 33 *voluntary admissions*, mostly for chronic alcoholism. These were not serviced by GSP. San Francisco had only three involuntary admissions (commitments), as shown in Table 2. This gives a *corrected commitment rate* of about 0.03 per 1,000 geriatric population in San Francisco.

ments of our aged to state mental hospitals from San Francisco. Optimistically, pre-GSP estimates hoped for a reduction from approximately 500 a year, by 50, perhaps even by 100 per year.

3. To promote better care generally for disturbed geriatric patients in the community by consultation with responsible persons and agencies which deal with the elderly, and by development of humane arrangements for their care without commitment.

Staff and Procedures

The staff, all state employees under the Department of Mental Hygiene, is composed of a half-time internist, a half-time psychiatrist, a supervising psychiatric social worker who functions as coordinator, a psychiatric social worker and a senior stenographer.

The function of the staff is to diagnose, to evaluate, to make recommendations, and to offer consultation; staff members are not involved in any continuing, active treatment program.

In providing these direct services the focus is on pre-admission and pre-petition screening. In this program unlike other screening programs in this respect, the patient is seen by members of the Geriatric Screening Project staff in his own home or setting, as in the famous Amsterdam (psychiatric) emergency service of Querido,* and not in the office. Imperative for success in such a project is a staff which has high tolerance for the depressing aspect of sick old people as well as a true dedication to serving them well.

Sources of Referral

Services are requested from many sources. All persons who inquire about a Petition for Mental Illness for any one over 65 at the office of the district attorney, or at IMPAC,† are routinely referred to the Geriatric Screening Project. Their concerns are about relatives, friends and tenants in apartments and hotels.

Their requests are usually made with intent of commitment in mind.

Example: A daughter contacts the district attorney's office to "take out papers." Her aging mother is exhibiting symptoms of mental disorder, such as

*Querido in Amsterdam . . . developed a system of mobile psychiatric teams which visit new patients in their homes in order to decide whether they need hospital care, or whether they can be referred to out-patient clinics or other care-giving agencies.^{25 26}

†San Francisco's Immediate Psychiatric Aid Center, located in the San Francisco General Hospital Psychiatric Building.

disorientation at night, wandering, getting lost, or accusations that people are stealing from her. The district attorney's office at once, before any petition is started, refers the daughter to the Geriatric Screening Project to determine whether a mental illness petition is necessary for the mother.

This referral procedure was suggested first to the committing judge (at the time, 1964, the Honorable Joseph Karesh). Use of it for a short trial period was fully endorsed. Soon it was recognized to be both sound and humane, and from then on the court refused to sign an order of detention on any aged person unless the order was first recommended by the project. Thus, intervention by the Geriatric Screening Project became possible before petition, and before admission to a psychiatric ward. We call this *pre-petition screening*. The patient thus is saved from the label and the trauma that go with the petition process. Formerly a very high proportion of elderly patients admitted to the psychiatric wards of the San Francisco County Hospital were eventually committed; and for those not committed it was difficult to find living accommodations in the community for patients once they had been in the psychiatric wards. Particularly is this true of the mentally disturbed "social isolate." (By a special survey we determined the same was true on the general medical wards for placement of all geriatric patients who are social isolates, even after the medical problems had been resolved.)

The Old Age Assistance Units of the local County Department of Social Services contribute the highest number of referrals. The social workers in this unit have enormous case loads, making extended attention to individual cases impossible. Many of their clients have neither friend nor relative to help the case worker obtain needed psychiatric and medical attention:

Example: A social worker refers a client whom she describes as mentally disturbed—perhaps demonstrating confusion or memory deficit, or paranoid ideas that interfere with adequate functioning such as sleeping, eating and competent control of bowel or bladder. The social worker may have already offered several remedial suggestions but the client has refused them all. At this point the worker refers the person to the Geriatric Screening Project. If the project recommends placement or other services in the community, the social agency ac-

cepts responsibility for implementing them.

Screening Procedures

The psychiatric social worker who first interviews the patient takes as complete a history as possible, including all identifying data. One or both members of the medical staff then makes a home visit, assisted by the social worker whenever possible. The time spent at the home runs about an hour, but may range from ten minutes (rarely) to well over two hours. Project members find the home visit important. The patient is more at ease and relationship is better established. On the home visit the physician can determine if, in fact, the patient does have food in his larder for an adequate diet, if there has been carelessness with matches, gas, water and electricity, if he has adequate control of bowels and bladder, and if he has gross systemic disease contributing to his mental illness.

At the home visit both a psychiatric and a physical inventory are made to the extent deemed important for the specific situation. In most cases, decision and recommendation are made before the investigators leave the patient's home. These are carefully discussed with the patient, if he is up to understanding them, and also with the responsible adult in charge if he is present. In some of the more complex situations decision is withheld until the client's case is fully discussed, in conference, by the Geriatric Screening Project staff. But in many cases the situation is in so critical a stage that decision and recommendation must be made and implemented without delay.

Geriatric Screening Project recommendations are almost uniformly welcomed and accepted gratefully.

Alternatives to State Hospital Admission

Placement facilities have been carefully evaluated by the staff social workers. Patient activity programs at these facilities, the attitude of staff toward patients and relationships among staff personnel, as well as physical characteristics and nursing care, are of primary concern in the evaluations.

Economic factors are a major concern. Well-to-do and middle economic bracket patients usually can finance themselves or their relatives can provide the money needed. But clients in the lower bracket, those dependent on Social Security and on Old Age Security, have found first the advent

of Medical Assistance to the Aged (MAA), and later of Medicare and of Medi-Cal, a life-saving boon. Likewise these agencies have contributed significantly to the successful record of the project by making needed nursing home and general hospital and private physician care a reality.

Planning, in every case, must be suited to the needs of the individual patient, and must be both appropriate and practical.

Not infrequently mental incompetence of a client requires court appointment of a guardian or a conservator.

In most instances, the project transfers responsibility for carrying out recommendations to the persons or agencies who referred the client and carry responsibility for the patient.

It is unfortunate that close follow-up of the almost 1,300 elderly, disturbed persons served by Geriatric Screening Project in the last three years has been impossible because of the heavy demands on the small staff. However, it is inferred, that, in general, the decisions and placements were satisfactory because of the rarity of second referrals of clients who were served by Geriatric Screening Project.

Maintenance in Own Home

Maintaining the disturbed older person in his own home is the program of choice and has been found to be feasible in 44 percent of cases.* Experience has shown that elderly persons are more contented and satisfied when this arrangement is possible. Community resources are called upon to give supportive services and are invaluable. They include homemaker services, attendant care, Meals-on-Wheels, visiting nurse care and public health nursing services. For counseling or social recreation, referrals are made to social casework agencies, senior citizen centers and friendly visitors. Frequently, a consultation by telephone with the private physician of the patient is indicated, and Geriatric Screening Project suggestions are usually accepted.

Out of Home Placement

Many of the patients served by Geriatric Screening Project require partial care and supervision best supplied in a good boarding home. For these, the staff makes careful selection to obtain the best possible placement. The total needs of the person

are considered and placement is never made for the convenience of the Geriatric Screening Project, or simply because a boarding home happens to have a vacancy. The personality or functioning of the caretaker with regard to understanding and coping with bizarre conduct of the client is a first consideration. Services that are available, such as assistance with needed personal care, are an important consideration. Geriatric patients not requiring skilled nursing services but only partial care and who present no serious behavior problems, get along adequately in the boarding home if the home is selected with his particular needs in mind. Some 8 percent of the Geriatric Screening Project clients were placed in boarding homes.

Nursing homes, or convalescent hospitals, which have demonstrated their ability successfully to manage the more confused, disoriented, wandering, and often cantankerous and demanding person are used for placement of patients of that order, as well as for patients requiring regular and skilled nursing services. Thirty-four percent of the patients were placed in nursing homes.

General hospitals have been used for the 10 percent of the patients found to have systemic medical problems. Patients were placed in private hospitals under private physician care, or were placed in the San Francisco General Hospital for general medical or systemic problems. Patients with more serious psychiatric illness have been referred to private psychiatrists, to day treatment centers and to hospitals with in-patient psychiatric services.

Involuntary Placement

A relatively few patients are a danger to themselves or to others; for these the project staff recommends Petitions for Mental Illness. On the court's acceptance of the petition, the patient is taken into the psychiatric ward at the county hospital, where he must remain for further evaluation, treatment and appropriate placement. Removed from their usual environment, and under the improved psychiatric treatment now available, these persons usually become much more amenable to accepting the recommended type of living arrangement. The committing judge, before whom all patients on petitions must appear, often discusses the proposed placement with the patient, reinforcing the staff recommendations.

The prestige of the court has proved valuable for patient-acceptance of recommended place-

*Percentages cited in this section relate to the 1,290 clients screened through GSP in the years 1965-6-7.

TABLE 2

	7/60-7/64 Average per Year	1965	1966	1967
Geriatric-Psychiatric Admissions to SFGH...	719	473	331	259
Geriatric Commitments ...	486	40	12	3

ments outside their homes. Except for those few persons committed to state hospitals, all petitions are dismissed when appropriate placement is accomplished. Only 4 percent of GSP clients were committed in the three years.

Project Results

The achievement of the Geriatric Screening Project most in keeping with its primary objectives has been a dramatic and undreamed of reduction of inappropriate commitments of geriatric patients from San Francisco County to state mental hospitals. In 1963, the first year of the project, there were 473 aged persons committed from San Francisco. Over the four years just preceding the home-visit-evaluation program, (that is, from July 1960 to July 1964) the number of geriatric commitments had averaged 486 per year. In 1965 this number was reduced to 40; in 1966 it was further reduced to 12. And in 1967 there was a total of only three geriatric commitments of persons dealt with by GSP.

During the same time, admissions of the elderly even to the hospital psychiatric wards were also reduced. The preceding four-year average was 719 per year; in 1967 the total was 259, only 35 percent of admissions in pre-project years.

Three hundred and fifty-two persons were screened by the project in 1967. Of that number only three were committed, and all three had previous record of commitment. Twenty-six percent were placed in nursing homes, 10 percent in boarding homes, 11 percent in general hospitals for systemic diseases, 52 percent were maintained, with supportive services, in their own homes.

Some 79 of the clients were admitted to the psychiatric wards (on Petition for Mental Illness recommended by the Geriatric Screening Project) to be further evaluated before final disposition. There were 183 admissions that by-passed the

Geriatric Screening Project, and they are not included in these percentages.

Mrs. X's commitment, cited at the beginning of this communication, preceded the Geriatric Screening Project program by three months. What a world of difference there would have been for her and her family had there been just a three months' delay in onset. Of the 1,290 geriatric persons served by the project in the last three calendar years, only 55 needed commitment. Simple arithmetic suggests that during the last three years more than 1,200 persons like Mrs. X have avoided commitment.

REFERENCES

1. Leverton, Alan F.: Unpublished observations by the first psychiatrist on the Geriatric Screening Project: The Induction of Disorganized Mental States by Inappropriate Patient Care in a Psychiatric Setting, 1 July 1964.
2. Blau, D., Kettell, M., Arth, M., Smith, J. W., and Oppenheim, D.: Psychiatric Hospitalization of the Aged, *Geriatrics*, 21:204-210, June 1966.
3. Booth, R. S., and Swain, J. M.: Mental disorders of the aged, *Calif. Med.*, 98:320-324, June 1963.
4. Lowenthal, M. F., and Berkman, P. L.: Aging and Mental Disorder in San Francisco—A Social Psychiatric Study, Jossey-Bass, Inc., San Francisco, 1967, pp. 255-257.
5. Grace, H. A., Littlestone, R., Mills, A., and McFeely, P.: Screening the Mentally Ill Before Court Commitment, California Department of Mental Health, pp. 37-45, Dec. 1965.
6. *Ibid.*, pp. 30-53.
7. Lowenthal, M. F.: Lives in Distress; the Paths of the Elderly to the Psychiatric Ward, Basic Books, Inc., 1964, pp. 170-175.
8. Final Report on the Long-Range Plan of the Department of Mental Hygiene: Published by the Senate of the State of California, 28 Feb. 1963, pp. 9-11.
9. *Ibid.*, pp. 31-33.
10. Blenkener, M.: Prevention or protection? Aspects of social welfare services for the mentally impaired aged, Research paper, supported by HEW Grant #175, from Benjamin Rose Institute, Cleveland.
11. Reference 8, p. 11.
12. Reference 8, p. 22-23.
13. Reference 8, p. 22.
14. Reference 8, p. 23.
15. Epstein, L. J., and Simon, A.: Organic brain syndrome in the elderly, *Geriatrics*, 22:145-150, Feb. 1967.
16. Wolff, K.: Psychiatric evaluation of geriatric patients on an outpatient basis: Preliminary study, *J. Amer. Geriatrics Soc.*, 6:760, 1958.
17. Wolff, K.: Geriatric Psychiatry, Charles C Thomas, Springfield, p. 27, 1963.
18. Reference 8, p. 23.
19. Kidd, C. B.: Criteria for admission of the elderly to geriatric and psychiatric units, *J. Ment. Science*, 108:68-74, 1962.
20. Simon, A., and Cahane, R. B.: The acute brain syndrome in geriatric patients, *Psychiat. Res. Reports*, 16 May 1963, pp. 8-21.
21. Noyes, A. P., and Kolb, L. C.: Modern Clinical Psychiatry, W. B. Saunders Company, 6th Ed., 1964, pp. 142-143.
22. Freedman, D. K., Troll, L., Mills, A. B., and Baker, P.: Acute organic disorder accompanied by mental symptoms; Intensive treatment in general hospitals for patients who suffer from acute brain syndrome, California Department of Mental Hygiene, pp. 1-21, Dec. 1965.
23. McDonald, C.: Treatment of the mentally disturbed geriatric patient, *Geriatrics*, 23:168-175, Jan. 1968.
24. Department of Mental Hygiene, Biostatistics Section, 4 Feb. 1964 and September 1964: Admissions of Patients, Aged 65 and Over, to State Hospitals for General Psychiatry, by County—Rates per 1,000 county population aged 65 and over, for years ending 30 June.
25. Caplan, G., and Caplan, R. B.: *In Comprehensive Textbook of Psychiatry*, Alfred M. Freedman, Williams and Wilkins Co., Baltimore, 1967, p. 1507.
26. Querido, A.: Experiment in Public Health, *In Bulletin World Federation of Mental Health*, 1954, #6, pp. 203-216. (Also abstracted in *Psychological Abstracts*, Vol. 29, 1955, p. 675.)

Rubella

Some Comments on the 1964-65 Epidemic in California

DAVID S. KLEINMAN, M.P.H., BELLE DALE POOLE, M.D., GWENDOLYN M. BECKMAN, A.B.,
MARJORIE F. HAMMERSLY, B.A., AND THEODORE A. MONTGOMERY, M.D., M.P.H., *Berkeley*

■ *The rubella epidemic of 1964-1965 resulted in the birth of a group of children with defects of vision, of hearing or of the heart. In this study of cases known to five Los Angeles agencies, it was found that about half of those affected have more than one defect. Findings demonstrate a need for more sensitive communicable disease surveillance and for the development of services for the multiple handicapped child.*

THIS IS A REPORT of a small and limited survey of some of the consequences of the 1964-1965 rubella epidemic in California. The survey was conducted to provide information regarding deficits and needs in the public health program. Because of the small number of cases studied and the manner in which they were selected, survey data cannot be considered definitive. It may be useful, however, in demonstrating the need for additional means of communicable disease surveillance and for special services for the multiple handicapped child.

Method

Study cases were identified by a medical social worker who reviewed the records of five agencies in the Los Angeles area. Information was gathered on children born between October 1962 and March 1966 with hearing, speech, eye or heart defects (or mention of maternal rubella) seen by these agencies before January 1967. The agencies were a hearing and speech center operated by a voluntary agency, three hospitals serving children who had

ocular or cardiac handicaps, and the State Department of Education's program which provides visiting teachers for the blind. Information was obtained from agency records about specific diagnoses and whether there was a history of rubella during the mother's pregnancy. Also, the problems faced by these facilities in serving this group of children and their families were discussed. It became apparent that the management of children with multiple handicaps was difficult for agencies that were prepared to deal only with single handicaps. Descriptive information was obtained through interviews with 13 of the families whose children had more than one defect.

Description of Cases

A total of 215 cases meeting survey criteria were found in the agencies' records, and they were classified according to the presumed cause of the patients' handicaps:

151 had defects due to rubella (record noted rubella as etiologic factor, based on maternal history or child's clinical syndrome).

45 had defects possibly due to rubella (records did not state rubella but it was considered possibly a factor by two reviewing physicians).

From the California State Department of Public Health, Berkeley.
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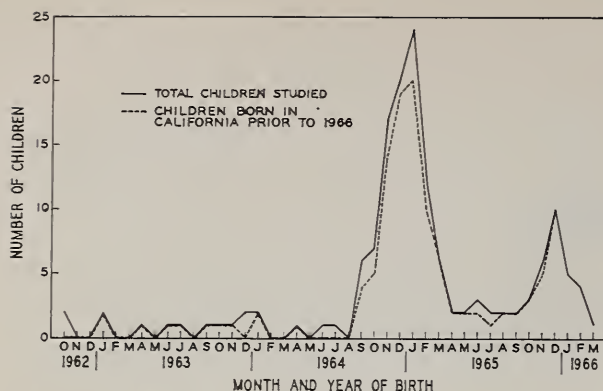


Chart 1.—Month and year of birth of children with defects attributed to rubella.

19 had defects which reviewing physicians considered either not due to rubella or of very questionable relationship to rubella.

It was decided not to include the “possible” or “questionable” cases because of the ways in which they differed from the 151 cases in which rubella was considered the cause of handicap.

The distribution of the birthdates of the 151 children in whom rubella was a factor followed an “epidemic curve” (discussed in a later section). This was not true of the cases considered possibly due to rubella, or of those which were questionable (see Charts 1 and 2). Only 11 percent of those who had handicap related to rubella were born before September 1964—that is, with the first trimester occurring before the epidemic year 1964. In approximately 42 percent of the “possible” and about 63 percent of the “questionable” cases, birth was earlier than the epidemic year 1964.

While almost half of the patients with handicap attributed to rubella had more than one defect recorded (Table 1), only one of the 45 in the “possible” and two of the 19 in the “questionable” category had more than one.

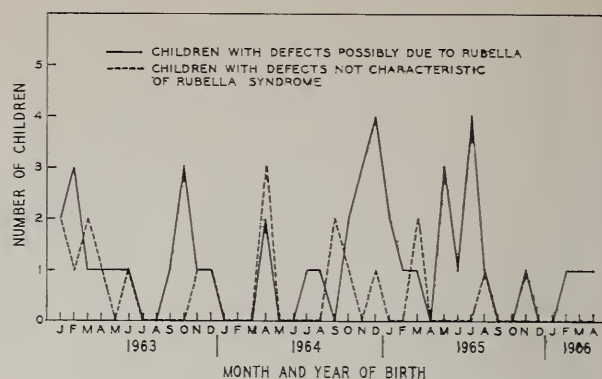


Chart 2.—Data on children with defects possibly due to rubella and those with defects not characteristic of rubella syndrome, related to month and year of birth.

It appeared, then, that these two categories should not be included and the analysis here is limited to the 151 cases in which rubella was presumptively established as the cause.

Table 1 shows the types of defects found among children in the study group. Seventy of them had two or more defects involving the heart, vision or hearing; of the 70, 41 had additional defects or were observed to be slow in physical and mental development. Among the children with only one defect of the heart, vision or hearing, defects in hearing were the most frequent (65 cases).

Age of the patient when he first came to one of the participating centers varied with the type and number of defects. In general, patients with more than one condition and those with heart defects were known to agencies earlier than those requiring care for eye and hearing defects only (Table 1). Of the children with multiple defects (and whose records included date of first visit or admission), 82 percent were seen in their first year, compared with only 25 percent of children with no other defect than deafness recorded.

Type of Defects	Age At First Visit Or Admission			
	Total	Under 1 Year	1 Year or More	Not Recorded
Total Children in Study*	151	80	58	13
Defects of the Heart, Vision, and/or Hearing†				
Multiple Defects	70‡	54	12	4
Single Defect	76	21	46	9
Heart only	6	5	1	
Vision only	5	2	2	1
Hearing only	65	14	43	8
Other Congenital Malformations	4	4		
Not Recorded	1	1		

*Includes children born from October, 1962 to March, 1966 who were known to at least one of five agencies in Los Angeles County before January, 1967.

†Includes children with additional congenital malformations and/or retarded mental and physical development.

‡Children with multiple defects include 60 with heart, 55 with vision and 43 with hearing defects.

TABLE 2.—*Occupation Group of Fathers of Children with Defects Attributed to Rubella Born in California before 1966*

Occupation Group of Father	Total Children Born in California Prior to 1966		At Least One Parent Born in California		Neither Parent Born in California		10 Percent Sample All Live Births California, 1959
	Number	Percent	Number	Percent	Number	Percent	
Total Children in Study*	120	100.0	75	100.0	45	100.0	100.0
Professional	18	15.0	11	14.7	7	15.6	7.9
Technical, Administrative, Managerial	21	17.5	14	18.7	7	15.6	11.7
Clerical, Sales and Skilled	37	30.8	24	32.0	13	28.9	31.6
Semiskilled	22	18.3	14	18.7	8	17.8	18.9
Laborer (Except farm and mine)	10	8.3	7	9.3	3	6.7	10.3
Farm Laborers and Foremen							3.4
Farmers and Farm Managers							1.2
Student	5	4.2			5	11.1	2.1
Military							10.6
Not Recorded, Unknown	7	5.8	5	6.7	2	4.4	2.3

*Includes children born from October, 1962 to March, 1966 who were known to at least one of five agencies in Los Angeles County before January, 1967.

Of the 151 patients, 12 died before the records were reviewed in January 1967.

California birth certificates were available for 120 of the children born before 1966. From a comparison of father's occupation (Table 2) of these children with the occupations of fathers in all live births, it appeared that the study group included a slightly larger proportion of children born to upper and middle income parents. This is probably due to the survey method, which used records of private agencies and hospitals which serve handicapped children: they are more likely to be utilized by the upper and middle socio-economic groups than by low income families.

Study findings cover three subject areas, which we will discuss separately:

1. Epidemic curves plotted from the birthdates of study cases.
2. Experience of patients and families in obtaining services.
3. Estimate of numbers of children born with defects as a result of the 1964-1965 rubella epidemic in California.

Epidemic Curves

Findings

When year and month of birth were plotted for children with defects attributed to rubella, there was a very definite pattern, with the major peak in January 1965 and a smaller peak in December 1965 (Chart 1). It would appear that the handicapped children we studied were the products of conceptions which occurred during two epidemics, one peaking in the late spring of 1964 and the other in the spring of 1965.

It should be noted that the smaller size of the later peak is probably related to the timing and method of studying the cases. Even among children with more than one defect of the heart, vision or hearing, 18 percent were not seen by survey agencies until after they were one year of age. Among the largest group—children needing care primarily for a hearing loss—three-fourths were not seen until after the first year.

Since records were reviewed in December 1966 and January 1967, affected infants born in late 1965 and early 1966 had only one year or less for referral to a center and inclusion in the study. So it may be assumed that if these infants had gained the same time interval for admission to the study as those born around January 1965, the second peak around December would be as high as the first.

A question that arises is: Were these infants affected by epidemics which occurred in California or did they represent infections to mothers elsewhere, who then migrated to California before delivery or brought their infants here? The eastern and central states experienced a severe epidemic in 1964 which was not observed to the same extent in Washington and Oregon (the only two Pacific states reporting rubella to the National Communicable Disease Center at that time) until 1965.⁴

Migration seems an unlikely explanation for the two epidemic peaks. Of the 141 children born before 1966, 120 were born in California, practically all of them in the Los Angeles area. (Certificates for the 1966 births were not available at the time of the study.) Thus, 85 percent were born in Cali-

fornia, and they did not appear to be children of recent migrants: in 75 cases one parent and in 25 cases both parents were born in California. This does not exclude the possibility that these mothers were out of state during early pregnancy. No information on travel was available for the total study group, but none of the 13 mothers interviewed had been out of California in the early months of pregnancy.

When the year and month of birth of California-born infants were plotted, two peaks were observed as with the total group (Chart 1); this was also true for infants with one or both parents born in the state.

The California-born infants studied were almost entirely residents of the Los Angeles area and perhaps inferences should be limited to that area. However, since the county includes almost 40 percent of the state's population, it is not unreasonable to assume that a rubella epidemic in Los Angeles would spread rapidly to show a similar pattern elsewhere in the state.

Chart 2 shows the distribution of birthdates of 45 children whose defects were possibly due to rubella, and of 19 children with conditions not characteristic of the rubella syndrome. These dates appear to be more randomly distributed than those in which rubella relationship was better established, although the "possible" cases seem to have a small increase clustered around November and December of 1964.

Discussion

During the 1964 epidemic in the eastern and central parts of the United States, an increase in cases was reported by Oregon and Washington to the National Communicable Disease Center, but the full impact was not apparent until 1965. In California, with a voluntary and fragmentary reporting system of cases seen by physicians, 2,500 cases of rubella were reported for 1964 compared with 10,500 for 1965. While the 2,500 cases that were voluntarily reported in 1964 reflected to some degree the occurrence of an epidemic, a comparison with the 10,500 cases reported in 1965 might indicate that the rubella epidemic elsewhere in the nation did not reach the West Coast in full intensity until 1965. This conclusion is contradicted by the findings of the present study, since the birthdates of affected children suggest an epidemic in 1964 of possibly the same intensity as that in 1965.

In 1966, rubella was made a reportable disease in California by the State Board of Health. But even with compulsory reporting, there still can be a significant lag between the occurrence of an epidemic and its recognition. Many of the rubella symptoms may be confused with those of other conditions. The presence of a known epidemic might influence the physician toward a diagnosis of rubella—all other factors being equal—but this would hardly speed up the recognition that an epidemic exists and the institution of plans to cope with the consequences.

Making laboratory diagnostic procedures more available would help but they are expensive and time-consuming and perhaps it is neither logistically possible nor economic to provide diagnostic tests in every case of suspected rubella. The practicing physician is most interested in procedures that directly bear on the treatment of his patient, and probably would order laboratory tests only where a clinical decision is involved, as in the case of a pregnant woman.

In addition to general reporting of cases, it would be helpful to establish surveillance posts in strategically located medical centers interested in definitive evaluation and diagnosis of diseases of current interest. The centers would be those serving populations at particular risk, or strategically located. They might include university student health services and hospitals with large maternity and outpatient departments. Frequently the first indications that an epidemic is in the making are apparent at such centers. If this intelligence could be brought into focus through provision of laboratory services and collation of information, the intervals between the disease outbreak and its recognition, and the development and implementation of plans for managing its consequences, could be considerably shortened.

Experiences of Patients and Their Families

Findings

Because no single facility has the wide variety of very specialized medical, testing, counselling, referral and educational services needed by those with multiple handicaps, the families of the 151 children studied had sought medical and rehabilitative care from numerous sources.

Information from the five agencies surveyed showed that 75 percent of the parents had been served by at least two or more community agencies

and 30 percent had used at least three or more, in addition to private physicians and other resources.

An insight into the problems of obtaining and providing care for these children was obtained through interviews with parents of 13 of those with multiple malformations attributed to rubella. The group was made up of families of children who were currently receiving services from the speech and hearing center. The records of the first 15 children requiring services for more than one defect, who were born during the period covered by the study, were selected from the case files. Two families had moved and were not available. The remaining 13 were all willing to be interviewed. While the questions were essentially open-ended, they were planned to cover the following:

- What the family was told about the possible effects on the newborn of rubella during pregnancy.
- What information was given the family on the patient's handicaps at birth, and by whom the handicap was first noted.
- The sequence of treatment, including the facilities used, how selected, any changes, and reasons for changes.
- Problems encountered.
- Information given on long-range planning.

As the group was not made up at random, it cannot be considered representative, but some insight into the problems facing the family and the community was gained.

All 13 mothers reported having rubella early in pregnancy; of these 11 reported the disease to their physicians in the course of prenatal care.

Five were either given no information regarding the possible consequences or were told not to worry; of the six who were informed of possible consequences, three attempted to obtain an abortion but were unsuccessful in finding a physician or facility willing to perform one.

In all but one of the 13 affected children the congenital condition was noted by the family or physician before the child was three months of age. In ten of the cases it was detected before the child was six weeks old. In one case it was not diagnosed until after the child was one year old. However, only 64 percent of the total 70 children studied with multiple defects were seen at participating centers before the child was six months old. If the experience of interviewed parents is typical, this was because families visited one or several physicians before coming into the centers, either through "shopping around" or through referral.

TABLE 3.—*Children with Defects Attributed to Rubella—Problems Most Frequently Mentioned by Mothers with Regard to Handicapped Child*

<i>Problems Most Frequently Mentioned</i>	<i>Number</i>
Total Mothers Interviewed.....	13
No Problems Reported.....	1
One or More Reported.....	12
Having to Go to So Many Facilities for Care, Difficulties with Making Appointments, Difficulties with Transportation.....	5
Educational Materials Do Not Meet Needs of Multiple Handicapped.....	4
Conflicting Advice from Professional People.....	4
Resources Didn't Know or Didn't Suggest CCS as a Possibility.....	3
Lack of Long-Range Planning.....	3
Acceptance by Other Family Members.....	3

Of the 13 mothers interviewed, seven had been in contact with two or more community agencies regarding the handicapped child's problems; five had been to three or more. These contacts were in addition to medical care for the child's various conditions from numerous medical resources:

<i>Number of Medical Resources</i>	
Total mothers interviewed.....	13
Only one source.....	—
2.....	1
3.....	3
4.....	5
5 or more.....	4

In 12 cases the families had used three or more sources of medical care. This enumeration does not reflect the difficulties encountered in obtaining services, in coordinating the treatments prescribed, in understanding and carrying out the advice given, in determining what services and assistance are available, and using them if they are available. Table 3 summarizes the most frequent responses by mothers to the interviewer's questions about some of their problems.

The difficulties encountered by families (even in an urban area such as Los Angeles with many medical community resources) may be seen from summaries of two interviews, one with a family dependent on public assistance and public medical care, the other with a family which would ordinarily use private medical care.

1. The affected child was, at the time of interview, a three-year-old girl, the youngest of six children, all under 12 years old. The family was dependent on public assistance, as the father had

deserted before this child was born. During the pregnancy the mother and children contracted rubella. The mother was told at the clinic not to worry. At birth a heart condition was found and was successfully treated surgically at one month.

Soon afterward the mother noted that the baby did not respond to sound. On examination at her insistence, deafness was diagnosed and a referral was made to a center for speech and hearing defects. But family complications interfered. About that time the mother was found to have a malignant tumor, and operation upon her and continuing disability afterward made it impossible for her to get the baby to the clinic until she was about a year old. Many lapses occurred in keeping schedules, as various medical crises arose—the mother's, the patient's, and those of the other children. (The patient was also found to have an orthopedic defect requiring regular clinic visits, and a sister is thought to have epilepsy and must be taken to the neurological clinic regularly.) Transportation and the cost of maintaining a car to get to medical care is a big problem for this family.

The patient is well accepted by the family and the mother feels her biggest problem is "getting her to understand." The child is considered to be intelligent by the otosurgical group and personnel at the hearing center.

The mother was told that it is essential for the child to start school by age three; she is now over that age, but neither the public school nor the hearing center has a vacancy.

2. The patient was an 18-month-old boy at the time of interview. His family consists of his divorced mother, a three-year-old sister, his grandmother and a ten-year-old aunt. The mother said that during her pregnancy both she and her husband had had rubella, but possible effects on the unborn child were never discussed. No handicaps were reported to the mother at birth. But at three weeks a pediatrician diagnosed blindness and a heart murmur; the patient was later found also to have a hearing defect and brain damage.

At the time of interview, eight different physicians and clinics had been involved in the child's care: a pediatrician, three eye specialists, a cardiologist, a psychologist, and two hearing centers. In addition, the child had received physical therapy. There had also been contact with Crippled Children Services, the local health department, the visiting teacher to the blind, and mental hygiene clinics.

The mother discussed the difficulties she had had with the large number and the sequence of medical examination, with necessary cancellations of appointments, with agency policies which affected choice of physicians, and with the differing opinions among various sources of care—all during the child's first year of life. There had been no long-range planning, which causes the mother some concern, for she believes the child will eventually need a residential school of some kind. She said that other mothers of handicapped children with whom she speaks have told her of long waiting lists at institutions. She said the hospital has been unable to provide advice about future planning, and that "everyone says, 'Don't worry'."

Discussion

Multiple handicaps in a significant number of children can be anticipated as a result of maternal infections during the 1964-1965 rubella epidemics. Of the estimated 750 to 1,500 affected infants, perhaps 300 to 600 would have more than one defect. If our survey is valid, it is obvious that several community resources are needed to treat these children. The parents of such infants face considerable difficulty in coordinating treatment recommendations and putting them into effect.

It would greatly help if services, including overall case management planning and follow-up for multiple handicapped children, could be provided through a single agency, along the pattern of the two California regional centers for evaluation and treatment of mentally retarded children.

Perhaps they could not only be used as a model but their functions extended to include such services for multiple handicapped children as evaluation, outlining a broad program of treatment, and arranging the use of available community resources for the specific services required. This would relieve the family of the decisions—which are essentially medical—regarding treatment priorities and coordination.

As with the mentally retarded, it is apparent that schools will need to provide special education facilities and services.

The value of the services would be significantly enhanced by making them available at an early age, before admission to school, and in pre-school programs. Even in these programs there is too often a lack of appropriately trained professional personnel to provide special education services.

Experience in the treatment of multiple handi-

capped children is limited, and it would be inappropriate here to discuss specific measures at great length. But it should be recognized that this problem is with us and requires attention.

Estimates of Number of Children Handicapped

Sever and coworkers,² reporting on a study of 6,000 women pregnant during the January-June 1964 epidemic (mostly in the eastern and central states) noted that by laboratory tests 9 percent of women reporting exposure to rubella in the first trimester had experienced infections, one-third of which resulted in clinical symptoms. While 10 percent of the women examined reported exposure in the first trimester, only 45 percent of the women in whom clinical rubella developed during the first trimester had been aware of—and had reported—exposure. From this it might be concluded that the actual exposure rate in early pregnancy during the epidemic was approximately 22 percent (10:45) of all pregnant women in their first trimester: Since 9 percent of women exposed showed infection, it can be estimated that approximately 2 percent of all pregnant women experience clinical or sub-clinical infection during the first trimester in an epidemic period.

Approximately 184,000 live births occurred in California during the months of September 1964 through February 1965. The first trimester of the gestation period in those infants occurred during the first six months of 1964, when presumably the epidemic was extant. Assuming an attack rate of 2 percent of infections during the first trimester for pregnant women in an epidemic period, there may have been an estimated 3,680 women with rubella infection during the first three months of pregnancy in California during the epidemic year of 1964, and perhaps a similar number in 1965. The reason an epidemic occurred in both 1964 and 1965 may have been that the first was not severe enough to build up a sufficient number of immune persons during that year to prevent its recurrence during the second year, particularly since there is evidence that infected infants remain carriers for up to six

months and serve as a reservoir of reinfection.¹ We might therefore revise our estimate downward to around 6,000 mothers with rubella infection in the first trimester during 1964 and 1965 (that is, 3,000 per year) of which perhaps 2,000 to 3,000 may have had clinical symptoms.

If we assume, as appears reasonable, that 25 percent of infants born to mothers with rubella in the first three months of pregnancy have a congenital malformation, we would estimate that around 750 to 1,500 malformed infants were born as a result of the recent epidemics of 1964 and 1965. While these estimates cannot be considered as accurately or even approximately giving the incidence of first trimester rubella, they do provide us with an order of magnitude which may be useful in planning.

On the basis of Sheridan's study of children whose mothers had rubella in early pregnancy, it is further estimated that 40 percent of the 750 to 1,500 affected children would have multiple malformations.³ Of those with one or more defects:

1. One-third would have heart defects.
2. One-third would have vision defects.
3. Sixty percent would have a significant hearing loss, including a large proportion (40 percent) in which the loss was not detected until age eight or over.

In the present study, the incidences of heart, vision and hearing defects were similar to those in the Sheridan group (Table 1). These are very general estimates but they provide some idea of what might be expected from the rubella epidemics of 1964 and 1965.

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REFERENCES

1. Schiff, G. M., Dine, M. S.: Transmission of rubella from newborns, *Amer. J. Dis. Child.*, 110:447-451, Oct. 1965.
2. Sever, J. L., Nelson, K. B., Gilkeson, M. R.: Rubella epidemic, 1964: Effect on 6,000 pregnancies, *Amer. J. Dis. Child.*, 110:395-407, Oct. 1965.
3. Sheridan, Mary D.: Final report of a prospective study of children whose mothers had rubella in early pregnancy, *Brit. Med. J.*, 1964, 2:536-539, Aug. 1964.
4. U. S. Department of Health, Education, and Welfare, National Communicable Disease Center: Morbidity and Mortality, 16:248-251, 29 July 1967.

Specific Learning Disorders

Natural History and Current Views

LOUISE TAICHERT, M.D., *San Francisco*

■ *Each professional, whether pediatrician, neurologist, psychiatrist, psychologist or teacher, in evaluating behavioral, neuromuscular, and emotional factors with the tools of his discipline, can arrive independently at very similar views regarding etiology and diagnosis of learning and language disorders. Even though this is possible, it is essential to have the many disciplines work together. This manner of sharing information is not only supportive to the patient, but to the physician as well.*

The pediatrician's role does not stop, however, with the diagnosis, but continues with the working through of problems that the child and parents present to one another.

AS KNOWLEDGE accumulates about childhood learning and language disorders, it becomes increasingly difficult to keep in touch with recent thought and developments in this field. Part of the difficulty arises out of diversity of professional interest and the resulting scatter of information on the subject among journals of neurology, psychology, education and pediatrics. Oddly, the pediatric journals seem to print less on this subject than the others mentioned. Specific learning disorders are discussed in the literature from many different professional points of view, not only with regard to early recognition and management, but to basic research in cognitive processes.

Review and clarification of the professional relationships involved in the care of children with specific learning disorders should bring about a greater understanding of the scope and meaning

of these conditions. Essential to appropriate care is a clear definition of the problems as well as knowledge of what happens to these children and their families once the diagnosis is made. The problems of children with specific learning disorders are often multiple and pervasive, expressed in disruptions of child development, social adaptation, function of family dynamics and demoralization of the child and parents.

Learning problems in general may be the result of emotional or neurological dysfunction, or a combination of both. This communication is concerned with "primary learning disorders"—also known as specific learning disorders, or dyslexia—in contrast to learning problems secondary to emotional disturbance or learning problems secondary to general mental retardation. It is essential for the pediatrician to be skilled in the differential diagnosis of these problems. The pediatrician should play an early prominent role in coordinating, assimilating, and translating the findings of the many

From the Department of Pediatrics, University of California Medical Center, San Francisco.

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Reprint requests to: 3600 California Street, San Francisco 94118.

disciplines to the family and child. After this is done a slow process of helping the family accept the findings begins. The interchange with other professionals active in the care of the child—social worker, neurologist, psychiatrist, psychologist, speech and language pathologist, education consultant and teacher—is intrinsic to the process of understanding these problems. School problems have come to involve the pediatrician in an area previously left to schools, psychiatrists or psychologists.

Learning Disorder

What is a specific learning disorder? It is an expression of neurological dysfunction, many times referred to as cerebral dysfunction. It may be acquired (as a result of neonatal or postnatal morbidity) or inherited. The latter, of genetic origin, more frequent in males, is termed primary or developmental dyslexia. Dyslexia is a disorder of reading. However, it is a term which has been widely used to mean a specific disorder of language, written or spoken, occurring in children with normal intelligence, involving one or more of the processes of visual or auditory perception, visual-motor ability, visual memory, visual sequencing, and auditory discrimination or memory.

Natural History

The child with a learning disorder comes to the pediatrician with a "hidden problem," often obscure to parents and teachers alike, but nevertheless very real for the child. Since the problems springing from them are obscure and subtle, learning disorders are often difficult to recognize and accept. It is around the child's and family's acceptance of a handicap that the physician must work. Not only does the pediatrician act as a skilled diagnostician, he acts as the counsellor and therapist for troubled children and their families. It is not enough to make a diagnosis, recite the literature and write letters to schools and referring physicians; it is important to follow the children with their families in an effort to help them work through their confusion and despair.

It is essential to identify the problems early. Once the problems are clearly defined, identified and brought out in the open, the patients and families are given an opportunity to express their feelings and act in a productive, rational manner.

Children with learning disorders present themselves to the physician in many different ways, that

is, with somatic complaints of headache and gastrointestinal disturbance, or with evidence of psychological stress and family dysfunction. By the time these children and their parents reach the physician, elaborate systems of defense, such as denial, despair or projection, have been established in an attempt to deal with the problems at hand. The physician therefore must be aware of family dynamics and the "natural history" of learning disorders to effectively assist these children and their families.

Some of the questions the pediatrician might ask himself are: What does *this* handicapped child mean to *this* family? Is the family using the handicap for maintenance of homeostasis of family function?¹ What meaning does this handicap have for the family in relation to the school and community? In this regard it must be borne in mind that the status of the family is often viewed by the school and community through the child's performance at school.

In reference to the "natural history" of this problem, one can see the problems shift from the child or "identified patient"¹⁶ to a whole spectrum of family-oriented problems, many times having to do with the parent's own feelings of self esteem. Families have been seen to use the child's problems in many different ways. One example of this can be through the use of many family survival myths¹⁰: "If it weren't for Billy, everything would be fine." This becomes a convenient way for families to direct attention from more serious painful family problems to the problems of the child.

It is interesting to see what happens to these children and their families. Many times the learning problem is unrecognized until the time the child enters school. Until entering school the child may have been considered "normal," having met many of the milestones of intellectual growth and social behavior. But, in going back in the history of many of these children, one often finds evidence of slow onset of expressive language, clumsiness, hypotonia, hypertonia, hyperactivity, irritability or impulsivity, to name a few of the symptoms that commonly appear.¹⁴ It is only after the child enters school that difficulties arise out of his inability to meet the academic tasks at hand. Parents and teachers may describe him as inattentive, hyperactive, a dreamer, or unable to take instructions.¹⁹ Parents begin to blame the child or the teachers by implication of motives—"If you'd only try harder" or "If you weren't so lazy," or "If

Billy only had a good teacher." If the use of blame proves ineffective, parents try to find a simple diagnosis: "Maybe his vision or his hearing should be tested." All the while he is trying to do what is expected of him during the school day and is experiencing repeated failure.

At times parents unwittingly give a child an inappropriate sense of power by saying "You're just doing this to hurt me," and the child soon learns that this is a way he can manipulate his parents. A covert power struggle results and may further exaggerate the problem. The physician therefore sees parents in all stages of confusion. After the parents go through phases of feeling despair, using blame, and arriving at a simple diagnosis, they go to a simple solution: "Everything will be fine when Billy learns to read." By this time, however, what was once a simple learning problem has become compounded by a feeling of worthlessness in the child, and a family desperately attempting to deal with its own disappointments.*

Each family has its own standards, rules and expectations, and it is interesting to see how differently one family views a learning problem than does another. If expectations are great within a family, the child fares less well than in a family where expectations are not so great. If risk-taking in the family is dangerous—that is, if there is little room for the child to make mistakes—he may soon stop trying and after awhile stop caring.

Parental concerns about causes are often brought out by the physician's question: "How do you see your child's problem?" However their questions are worded, parents seem to ask one of two things: "Is my child emotionally disturbed?" or "Is my child neurologically handicapped?" In the recent past children with primary learning disorders were thought to have learning problems secondary to emotional disturbance. Worst of all, parents often were made to feel blame and responsibility for their child's problems.

A learning disorder becomes a family problem, not just a problem of the child. Pediatricians are beginning to play a more active role in counselling and in pediatric mental health. There is a need for increased emphasis in pediatric training programs on problems of growth and development and mental health.¹¹

*This train of events was originally described in a personal communication by Alan Leveton, M.D., University of California Medical Center, San Francisco.

Professional Roles

A question frequently asked by physicians is one having to do with understanding and interpretation of psychological test results and the role of the psychologist: "Since psychologists make the diagnosis, why is a pediatrician involved with this problem at all?" Also, "Is there any one psychological test or specific scatter [profile] of subtest items on the Wechsler Intelligence Scale for Children [WISC] that is or can be diagnostic of learning disorders?"

The psychologist's developmental assessment is of great assistance in making a proper evaluation, and provides valuable information about the child's intellectual function and social adaptation. There appears to be no single psychological test or subtest scatter on the WISC which by itself is diagnostic or pathognomonic of a specific learning disorder.^{2,20} As in other areas of medicine, the child must be viewed as a whole. In this particular situation a great number of tests are used that evaluate the various processes of learning and the status of the neuromuscular system. (See list adjoining.)

The psychologist uses standardized tests to assess intellectual, social and psychological function as well as determine the status of the youngster's different processes of learning—that is the processes involved primarily in the visual and auditory pathways of learning. He observes many of the processes of cognitive behavior and in this way obtains an impression of cerebral function with or without associated learning disorders.

Some of the Psychological Tests Commonly Used in Evaluation of Intellectual and Social Maturity and Function of Children with Specific Learning Disorders.

Intelligence:

Wechsler Intelligence Scale for Children (WISC)—

Verbal Scale:

1. Information
2. Comprehension
3. Arithmetic
4. Similarity
5. Vocabulary
6. Digit Span

Performance Scale:

1. Picture Completion
2. Picture Arrangement
3. Block Design
4. Object Assembly
5. Coding

Test Behavior:

Rapport, Motor Activity, Attention, Response to Failure, Problem Solving Methods, Task Needs, Attitude, Verbal Activity, Distractibility, Performance Speed, Response Control.

Educational Achievement:

Wide Range Achievement Test (WRAT)—

Reading Grade Level: word recognition

Spelling Grade Level: writing dictated words

Arithmetic Grade Level: pencil and paper solution of number problems

Oral Reading Tests: Grey Gilmore

Visual Motor Coordination Test:

Bender Gestalt Visual Motor Test

Detroit, Benton: Memory for Designs Tests

Developmental Form Sequence

Frostig Test of Visual Motor Coordination:

Eye-Motor Coordination

Figure Ground Discrimination

Form Constancy

Position in Space

Spatial Relations

Draw-A-Person

Auditory Tests:

Sentence Memory (auditory tracking)

Detroit Tests of Learning Aptitude

Wepman Auditory Discrimination Test

Projective Tests

Thematic Apperception Test (TAT)

"I" Sentence Completion Test . . .

Role of Neurologist

The relative importance of the neurological examination and certain neurological findings in respect to diagnosis of learning disorders is frequently misunderstood. Teachers and sometimes parents ask, "Has there been a neurological exam?" expecting a magic answer. Is there any one neurological finding that is diagnostic in itself of learning disorders? Such single findings as mixed dominance,⁶ abnormal pattern of hair whorl, poor finger position sense,³ or abnormal arm extension¹⁷ or head rotation have at some time been thought to be present only in children with learning disorders, or have had some special diagnostic value ascribed to them.¹⁵ Up to the present there appears to be no one specific finding that is in itself diagnostic.⁹

The neurologist arrives at the diagnosis of cerebral dysfunction with or without associated learning problems by viewing total function of the neuromuscular system.⁷ This can be done by assessing the type and quality of motor activity.¹³ He looks for dyspraxia, dyskinesia, synkinesia, confused laterality, confused body image,⁵ poor finger sense,³ or localization—to name a few signs of neurological dysfunction.¹⁸

It is possible to say what a learning disorder is as well as what it is not, and to define what one discipline does or does not do. To be sure, each professional, whether pediatrician, neurologist, psychiatrist, psychologist, speech and language

pathologist, or teacher could arrive at the diagnosis of a learning disorder independent of the others through their shared knowledge and common understanding of the problem.

The pediatrician approaches the problem by obtaining a detailed clinical history of growth and development, which includes a pertinent assessment of neurological and cognitive function. Of great help is the important contribution of Katrina deHirsh in her book *Predicting Reading Failure in the Preschool Child*.⁸ Her study of a group of preschool children who have been followed over a 20-year period shows a significant correlation between certain motor and cognitive skills and failure to read, or with a delayed onset of reading. The onset and quality of expressive language development, the child's use of words and ability to tell a story, his use of a pencil—that is, how it is held—and finally the child's ability to copy written symbols are of predictive diagnostic value.

Current Views of Remediation

Historically, in considering ways to remedy learning disorders clinicians' and research investigators' interests have shifted from *etiology*, to *process*, and finally to *analysis of the task*.⁴ There was a time when interest was directed mainly to the process.¹² It was felt that once the child's difficulty with a process was defined the management of this "disability in process" could be specific to that disability. For example, for a weakness or disability in the process of visual memory, teaching methods were focussed directly on overcoming this particular disability. Educators "taught to a disability" or to a weakness. Others held that methods of instruction should utilize or teach to the "strengths," that is, to the available capacity of the child, not his weaknesses or deficiencies. In any event, it is helpful for the clinician to identify these specific areas of disability, to consider both the strengths and the weaknesses in the child's overall learning ability. This manner of looking at things becomes helpful in interpreting the findings and the diagnosis to the parents and the child.

Most recently, Bateman¹ and coworkers developed another approach as an outgrowth of their development of the Illinois Test of Psycholinguistics (ITPA). Their theory is that regardless of the process one must teach to the task, and the task is reading. Reading is learning in two stages. Stage one is the stage of symbol recognition and conversion of the symbol to a sound. Stage two has to do

with comprehension of this sound, or, in other words, reading with meaning. They feel that reading is essentially an auditory skill; that stage one is a rote task that should be taught with phonic and auditory methods. It is their belief that, regardless of the child's individual weakness, whether auditory or visual, he will learn with auditory methods of remediation. This is analogous to a hematologist's approach to a bleeding disorder: He determines exact clotting factor deficiencies, but many different kinds of deficiencies respond to treatment with plasma.

REFERENCES

1. Bateman, Barbara: Analysis of Reading Disability, Curriculum Bulletin, School of Education, University of Oregon, Vol. III, No. 278, May 1967.
2. Bender, Morris B.: Disorders in Perception, Charles C Thomas, Springfield, 1952.
3. Benton, Arthur L.: Right-Left Discrimination and Finger Localization, Hoeber, New York, 1959.
4. Bereiter, C., and Englemann, S.: Teaching Disadvantaged Children in the Preschool, Prentice-Hall, Englewood Cliffs, New Jersey, 1966.
5. Berges, J., and Lezine, I.: The Imitation of Gestures, Heinemann, London, 1965.
6. Capobianco, R. J.: Ocular-manual laterality and reading achieve-

ment in children with special learning disabilities, Amer. Educ. Res. J., 4:133-138, March 1967.

7. Clements, S. D., and Peters, J. E.: Minimal brain dysfunction in the school age child, Arch. Gen. Psychiat., 6:185-197, March 1962.
8. deHirsch, K., Jansky, J., and Langford, W.: Predicting Reading Failure in the Preschool Child, Harper and Row, 1966.
9. Eisenberg, Leon: Reading retardation: I. Psychiatric and sociologic aspects, Pediatrics, 37:352-365, Feb. 1966.
10. Gehrke, S., and Kirschenbaum, M.: Survival patterns in family conjoint therapy, Family Process, 6:67-80, March 1967.
11. Gofman, Helen: Training the Physician in the Evaluation and Management of the Educationally Handicapped Child, 53-108, Educational Therapy, Vol. 1, Special Child Publication, Seattle, Washington, 1966.
12. Kephart, Newell: The Slow Learner in the Classroom, Charles E. Merrill Books, Inc., Columbus, Ohio, 1960.
13. Paine, R. S., and Oppe, E. E.: Neurological Examination of Children, Heinemann, London, 1966.
14. Pincus, J. H., and Glaser, G. H.: The syndrome of minimal brain damage in childhood, New Eng. J. Med., 275:27-35, 7 July 1966.
15. Salam, M., and Adams, R.: New horizons in the neurology of childhood, In Perceptives in Biology and Medicine, Vol. IX, No. 3, 384-419, Spring, 1966.
16. Satir, Virginia: Conjoint Family Therapy: A Guide to Theory and Technique, Behavior Books, Palo Alto, California, Revised Edition, 1964.
17. Silver, Archie A.: Postural and righting responses in children, J. Pediat., 41:493-504, Oct. 1952.
18. Steegman, A. Theodore: Examination of the Nervous System, Year Book, Second Edition, 1962.
19. Tomkins, Calvin: The Last Skill Acquired, The New Yorker, 14 Sept. 1963.
20. Wiener, G.: The Bender Gestalt Test as a predictor of minimal neurologic deficit in children eight to ten years of age, J. Nerv. Men. Dis., 143:275-280, 1966.

OFFICE DETECTION OF HYPERLIPIDEMIA

"A single cholesterol test will pick up 85 to 90 percent of hyperlipidemia, if one uses 250 mg and above as a cutting off point and if one has a reliable laboratory. . . . There will be some people who have hypertriglyceridemia without hypercholesterolemia . . . , and you will miss them if all you do is a serum cholesterol. But you can get around that to a considerable degree by a simple additional step, and that is to collect fasting serum with a good overnight fast — 15 hours is preferable to 12 hours — and look at the serum to see if it's turbid. If it's turbid, even though the cholesterol may be under 250 mg, the triglycerides are elevated, and you'll pick up about half or two-thirds of those [patients] with hyperlipidemia that you have missed. . . . If you want to know if the turbidity is endogenously synthesized triglyceride (or very low low-density lipoprotein) as distinct from alimentary chylomicron, there's a very easy way to find out. Put the turbid serum in the refrigerator and let it stand overnight. If a cream layer rises to the top of the serum, that is almost certainly chylomicron of alimentary origin. Either the person did not tell you the truth when he said he had gone without food for 15 hours or he has a true chylomicronemia with an inability to clear plasma even after 15 hours of fasting. . . . By the simple look at turbidity, plus an icebox test, plus a cholesterol, you can make the diagnosis in 95 percent of cases."

— JEREMIAH STAMLER, M.D., Chicago
Audio-Digest General Practice, Vol. 16, No. 35

Intussusception in Adults

R. J. STECKLER, M.D., A. SOURIAL, M.D., D. BASKETT, M.D.,
I. SCHAFFNER, M.D., AND V. DIDIO, M.D., *Thousand Oaks*

■ *Three cases of intussusception in adults were observed within a period of six months in a small general hospital. All the patients were over 65 years old and all were admitted to hospital with intermittent cramping abdominal pains. None appeared to be in acute distress. In all three, body temperature, pulse rate and hemogram were within normal limits. Diagnosis was made preoperatively after barium enema studies. Bowel resection with end-to-end anastomosis was done in all three cases, in two because of gangrenous bowel. The site of intussusception was jejunojejunal in one case, ileocecal in another and colorectal in the third; and the cause in all cases was tumor, benign in two cases, malignant in one. The patients recovered uneventfully except for incisional abscess and diarrhea of seven days' duration in one. In a review of literature it was found that the clinical features in these three cases closely paralleled those of other cases of adult intussusception reported in this country.*

INTUSSUSCEPTION IN ADULTS is not frequently encountered or reported in the medical literature. Because of its deceptive clinical manifestations and the high incidence of associated pathologic changes, it differs a great deal from intussusception in children. Unless promptly diagnosed and surgically repaired, the condition often is associated with morbidity and even mortality.¹ Frequently a malignant lesion is a further complicating factor.²

Incidence

That intussusception in adults, although uncommon, is not rare is evidenced by the admission of three patients with this condition in less than six months to a 65-bed general hospital serving a population of 40,000. MacNab³ in 1948 estimated

that 4.5 percent of cases of intussusception were in adults. In 1949 Wangenstein⁴ reported that approximately 75 percent occur in children under two years of age. Colter and Cohn¹ noted that 1,330 cases had been reported between the years 1892 and 1961. Roper⁵ calculated that one case of adult intussusception per 100 surgical beds should be encountered every 12 to 16 months. With the increase of government assistance health programs and with more aggressive surgical treatment in the aged population, it is expected that more cases in adults will be observed.

Etiology

In this country adult intussusception is most often due to an organic lesion, usually tumor and frequently malignant,² although this association was not observed by several investigators in Korea⁷ and Western Nigeria.⁸ Other relatively frequent

From the Conejo Vallejo Community Hospital, Thousand Oaks.
Submitted revised 22 July 1968.

Reprint requests to: Conejo Valley Community Hospital, 384 Erbes Road, Box 1155, Thousand Oaks 91360 (Dr. Steckler).



Figure 1.—Jejuno-jejunal intussusception due to small bowel tumor (benign).

causes are Meckel's diverticulum and nonspecific inflammatory processes. Twelve of 96 cases in one series² were idiopathic (as compared with 95 percent in children).^{1,3} In only six of the 12 could intussusception be reduced. Two factors seem necessary for production of intussusception—a relatively rigid segment of bowel (made so by tumor, inverted diverticulum, or edematous bowel secondary to inflammation) and a mobile segment long enough to permit telescoping.^{9,10} Polypoid and pedunculated tumors are particularly inclined to intussuscept. In children the location of the intussusception is ileocecal in 65 to 90 percent of cases, whereas in adults approximately one-third are in the small bowel, one-third are ileocecal and one-third are in the colon.²

Summary of Cases

CASE 1.—A 70-year-old Caucasian woman was admitted to hospital 28 February 1967 with a history of colicky upper abdominal pain following ingestion of food. The pain occasionally was relieved by emesis. Taking only liquids tended to avoid painful episodes. There had been weight loss of about 50 pounds in the preceding year. On examination the patient appeared to be in no acute distress. The rectal temperature was 37.5°C (99.6F), the pulse rate 86, respirations 20 per



Figure 2.—Ileo-colic intussusception due to small bowel tumor (benign).

minute and blood pressure 160/90 mm of mercury. The abdomen was soft and slight tenderness was noted in the right upper quadrant. No masses or organs were felt. Results of laboratory studies were within normal limits.

X-ray studies of the upper gastrointestinal tract done 3 March 1967 revealed a large sliding esophageal hiatus hernia and evidence of partial obstruction in the proximal jejunum. A small bowel series showed intussusception of a tumor in the jejunum, causing incomplete obstruction of the small bowel. At operation a jejunojejunal intussusception was found about 60 cm distal to the ligament of Trietz, led by a polyp 5 cm in diameter. The intussusception was reducible but segmental resection of the jejunum along with the polypoid lesion was deemed advisable. Pathologic sections were characteristic of inflammatory fibrous polyp. The postoperative course was uneventful.

CASE 2.—A 78-year-old Caucasian woman was admitted to hospital 14 June 1967 with a history of rather sudden onset of abdominal discomfort beginning a week before. She had passed several loose stools of normal color and twice had vomited bile-stained gastric contents. The episode subsided within 24-hours but three days later she began having cramping abdominal pains and passed sev-



Figure 3.—Colo-colic intussusception due to large bowel tumor (malignant).

eral loose stools. The pains continued intermittently until admission.

On examination the patient was observed to be obese and apparently not in acute distress. Rectal temperature was 37.5°C (99.6°F), pulse 92, respirations 20 and blood pressure 180/80 mm of mercury. The abdomen was slightly distended and generalized muscle guarding was evoked. Rebound tenderness was noted in the right lower quadrant. No masses were felt and no abnormalities were observed on rectal examination. Hemoglobin content was 10.5 gm per 100 ml of blood. Leukocytes numbered 10,800 per cu mm—74 percent polymorphonuclear cells, 21 percent lymphocytes, 3 percent monocytes and 2 percent eosinophils. There was a trace of occult blood in the stool. The clinical impression was possible acute appendicitis, with carcinoma of the cecum to be ruled out.

X-ray studies of the abdomen showed a mild generalized increase in small bowel pattern of a nonspecific nature. A similar examination two days later showed findings compatible with small bowel obstruction, and studies with barium enema the following day revealed a filling defect at the ileocecal valve which "may represent an intussusception."

At operation an ileocecal intussusception with

the head of the intussusceptum extending 3 inches into the colon was observed. A 3.5 cm ileal polyp on a long pedicle led the intussusceptum into the colon and was lying in the cecum. There was a Meckel's diverticulum 15 cm proximal to the intussusception. The intussusceptum was gangrenous. After partial reduction of the intussusception, a segmental ileal resection, a Meckel's diverticulectomy and end-to-end anastomosis were carried out. On pathologic examination the lesion leading the intussusceptum was described as inflammatory mucosal polyp.

The postoperative course was complicated by an incisional abscess and watery diarrhea which lasted several days.

CASE 3.—A 65-year-old Caucasian man was admitted to hospital 3 July 1967 with a history of diarrhea with bloody stools for six days. Until then he had had alternating constipation and diarrhea for two months. The past history was not contributory.

The patient appeared fairly well-nourished and seemed to be in no acute distress. Rectal temperature was 37.5°C (99.6°F), the pulse rate 96, respirations 20 per minute and blood pressure 150/80 mm of mercury. The abdomen was moderately distended and tympanitic to percussion. There was no rigidity, and no masses were felt. Mild tenderness was elicited in the right lower abdominal quadrant. The bowel sounds were hyperactive. Rectal examination revealed a 5 to 7.5 cm soft, round mass filling the rectal ampulla 5 cm above the anal verge. There was dark blood on the examining finger.

Laboratory studies: Hemoglobin was 13.1 gm per 100 ml and leukocytes numbered 11,500 per cu mm—71 percent polymorphonuclear cells, 18 percent lymphocytes and 11 percent monocytes.

X-ray examination of the abdomen showed changes consistent with large bowel obstruction, with the sigmoid colon the site. Barium enema filled the rectal ampulla and demonstrated an area of intussusception near the rectosigmoid junction with the head of the intussusceptum dipping into the rectal ampulla.

At operation the sigmoid colon was found to be intussuscepted into the rectum, and an area of gangrene encircled the bowel. The intussusception was partially reduced in order to perform a sigmoid resection and end-to-end anastomosis. On examination of the surgical specimen a 4 x 2.5 x 2.0 cm "cauliflower" mass attached to the rectum

mucosa was observed to be the cause of the intussusception. Pathologic examination revealed a Grade I papillary adenocarcinoma without stalk invasion.

The postoperative course was uneventful.

Discussion

Unlike pediatric intussusception, which usually comes to medical attention because of an acute episode with clear-cut findings, intussusception in adults often presents with bizarre symptoms of relatively long duration and has been variously diagnosed as appendicitis, ovarian cyst, regional enteritis, renal calculus, and ruptured atopic pregnancy.^{1,2}

In only 13.5 percent of a series reported by Dean and coworkers² were the first symptoms those of acute intestinal obstruction. One of the three patients reported herein (Case 3) was admitted with a clinical impression of mechanical obstruction of the large bowel, but in Case 1 the symptoms were consistent with peptic ulcer disease and in Case 2 with appendicitis. In a review of the literature—and in our own three cases—the most frequently noted symptoms at the time of first examination were intermittent colicky abdominal pain, increased by eating, and vomiting, diarrhea and loss of weight. Rectal bleeding may or may not be present. Two of the patients in the present report had vomiting and two had diarrhea, one with passage of dark red blood. A deceptive clinical feature is that the patient does not appear acutely ill. None of the three patients we treated had fever. The highest leukocyte count among them was 11,500 per cu mm, and the cell differential was within normal limits. Yet in two of the patients devitalized bowel was observed at operation. This deceptive incongruity was corroborated in other series.^{1,6} The most prominent physical symptom is moderate tenderness of the abdomen, sometimes with slight distention. There may be a palpable mass, as was the case of one of our patients, and in some cases a mass may be felt and later disappear.¹⁰ In three series that we reviewed, correct preoperative diagnosis was made in 23, in 29 and in 56 percent of cases. In two of the three

cases herein reported, correct diagnosis was made before operation and in the other it was strongly suspected. Early barium contrast studies of the gastrointestinal system can be very helpful in arriving at a correct diagnosis early.⁹ Delay in diagnosis and surgical treatment is associated with a decided increase in morbidity and mortality.¹

Gangrene of the bowel in two of the patients we treated may have been due at least in part to a delay of three days between the time of admission and the barium enema studies that confirmed the diagnosis.

Treatment consists of prompt surgical intervention. Seldom can reduction of hydrostatic pressure be accomplished, but if it can be it should be followed by bowel preparation and surgical exploration because of the high incidence of associated organic disease. Burmeister¹¹ stressed prompt operation in pregnant women especially, because of the high maternal and fetal mortality associated with delay. Even with prompt surgical intervention, resection rather than reduction is necessary in a high proportion of cases. Resection was done in two of the patients we treated, although as an elective procedure in one of them. If feasible, exploration of the bowel should be carried out, for in a few cases there may be tumors elsewhere than at the site of intussusception. If the patient is severely ill, a temporary ileotransverse colostomy with later resection may be indicated.¹

REFERENCES

1. Cotlar, A. M., and Cohn, I., Jr.: Intussusception in adults, *Amer. J. Surg.*, 101:114-120, Jan. 1961.
2. Dean, D. L., Ellis, H. F., Jr., and Sauer, W. G.: Intussusception in adults, *Arch. Surg.*, 73:6-10, 1956.
3. MacNab, G. N.: *British Surgical Practice*, Vol. 5, Butterworth, London, 1948.
4. Wangenstein, O. H.: Intestinal obstruction in, *In* Christopher, F., Editor: *Textbook of Surgery*, 5th Ed., W. B. Saunders Company, Philadelphia, 1949, pp. 1062-1064.
5. Roper, A.: Intussusception in adults, *Surg. Gynec. Obstet.*, 103:267, 1956.
6. Deterling, R. A., O'Malley, R. D., and Knox, W.: Intussusception in the adult with emphasis on the retrograde type, *Arch. Surg.*, 67:854-864, Dec. 1953.
7. Dietrick, R. B., and Lee, M. H.: Intussusception: A different clinical entity in Korea, *Surgery*, 57:651-654, May 1965.
8. Elebute, E. A., and Adesola, A. O.: Intussusception in Western Nigeria, *Brit. J. Surg.*, 51:440-444, June 1964.
9. Schatzki, R.: The roentgenologic appearance of intussuscepted tumors of the colon with and without barium examinations, *Amer. J. Roentgen.*, 41:459-563, Apr. 1939.
10. Bond, M. R., and Roberts, J. B.: Intussusception in the adult, *Brit. J. Surg.*, 51:818-825, Nov. 1964.
11. Burmeister, W.: Intussusception in adult: elusive cause of recurrent abdominal pain, *Amer. J. Digest. Dis.*, 7:360-374, Apr. 1962.

Ovarian Tumors

Histogenesis and Systemic Effects

H. FOX, M.D., *San Francisco*

■ *Sufficient histologic and embryologic information is now available to allow for a reasonably satisfactory histogenic classification of ovarian neoplasms. The majority of these tumors are derived from germ cells, sex cord-mesenchyme or the germinal epithelium. A few, such as the Brenner tumor, must still be classed as being of "uncertain histogenesis," for the cell (or tissue) of origin is not yet known.*

It is now realized that many ovarian neoplasms previously considered to be endocrinologically inert may, on occasion, be associated with either estrogenic or androgenic activity. This applies particularly to Brenner tumors, mucinous cystadenomas and serous cystadenomas. The common factor associated with such endocrine activity is luteinization of the tumor stroma.

Ovarian neoplasms usually manifest only local symptoms, but they may, on occasion, be associated with such unusual systemic effects as hypoglycemia, hypercalcemia or a hemolytic anemia.

THIS REVIEW PRESENTS a classification of primary ovarian tumors that is based on current histogenetic concepts; it is not proposed to discuss each tumor but to consider briefly only those neoplasms about which fresh information has accrued in recent years and to review also recent data concerning systemic manifestations of ovarian tumor.

A. Classification and Histogenesis of Ovarian Tumors

Germ cell tumors

The germ cell origin of teratomas is now widely

accepted for no other hypothesis can explain either the dominance of the gonads as a site for such neoplasms or the finding that whilst ovarian teratomas are invariably sex chromatin positive, those occurring in the testis may show either a male or a female sex chromatin pattern.⁴⁶ The question whether a teratoma develops by fusion of two haploid cells with neoplastic transformation of the resulting product or by parthogenetic division of haploid cells with later chromosomal reduplication has been much debated; this debate has been stimulated by the fact that teratomas usually have a diploid chromosome content but it has been pointed out² that neither of these two hypotheses need be invoked inasmuch as the ovarian germ cells, until immediately before ovulation, are in

From the Department of Obstetrics and Gynecology, University of California Medical Center, San Francisco.

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Reprint requests to: Department of Obstetrics and Gynecology, University of California Medical Center, San Francisco 94122.

TABLE 1.—*Classification of Ovarian Tumors*

1. *Of germ cell origin*
 - i. *Dysgerminoma*
 - ii. *Teratoma*
 - a. *Undifferentiated*
Embryonal carcinoma
 - b. *Partially differentiated*
Embryonic differentiation—teratocarcinoma
Extraembryonic differentiation—choriocarcinoma, endodermal sinus tumor
 - c. *Fully differentiated*
Benign
cystic teratoma
struma ovarii
mucinous cystadenoma
With malignant change
squamous cell carcinoma
malignant melanoma
thyroid adenocarcinoma
carcinoid tumor
2. *Origin from sex cord mesenchyme*
 - i. *Ovarian differentiation*
Granulosa cell tumor
Thecoma
Lipid cell tumor
 - ii. *Testicular differentiation*
Arrhenoblastoma
Sertoli cell tumor
Hilar cell tumor
 - iii. *Mixed testicular-ovarian differentiation*
Gynandroblastoma
3. *Origin from coelomic (germinal) epithelium*
 - i. *Via tubal differentiation*
serous cystadenoma
serous cystadenofibroma
serous cystadenocarcinoma
 - ii. *Via endocervical differentiation*
Mucinous cystadenoma
Mucinous cystadenocarcinoma
 - iii. *Via endometrial differentiation*
endometriosis
endometroid carcinoma
adenoacanthoma
clear cell adenocarcinoma
mixed mesenchymal sarcoma
rhabdomyosarcoma
4. *Origin from non-specialized stroma*
Fibroma
Fibrosarcoma
Lipoma
Hemangioma
5. *Mesonephric origin*
Mesonephroma
6. *Lymphoma*
Lymphosarcoma
Hodgkin's Disease
Burkitt tumor
7. *Of uncertain origin*
Brenner tumor
Gonadoblastoma
Adenomatoid tumor

the prophase of the first meiotic division and are therefore diploid.

The embryonal carcinoma, the teratocarcinoma and the benign cystic teratoma are now considered as simply representing different stages along the maturation pathway of a single neoplasm, and this

concept is supported by the finding that, in children, the average age at which teratocarcinomas occur is lower than that at which benign teratomas are found, whilst the average age of patients with an embryonal carcinoma is lower still.¹ The embryonal carcinoma is formed of undifferentiated cells similar to those found during the earliest stages of embryonic development, and further maturation may be toward extraembryonic or embryonic structures, the former giving rise to an endodermal sinus tumor or a choriocarcinoma. The endodermal sinus tumor is formed of loose, vascular connective tissue admixed with "glomerular-like" structures; it was originally thought that this neoplasm was a mesonephroma but the suggestion⁵⁰ that the histological appearances represent a reproduction of stages in the phylogenetic development of extraembryonic membranes is now more favored. According to this interpretation the connective tissue is homologous with the allantoic mesoderm of the labyrinthine placenta whilst the glomeruloid structures are the homologs of the yolk sac endodermal sinus of the rodent placenta.

Partial maturation of a teratomatous neoplasm into embryonic or adult structures gives rise to a teratocarcinoma or "solid teratoma." Such tumors are usually frankly malignant both clinically and histologically but a few solid teratomas appear sufficiently histologically mature to hardly merit the term "teratocarcinoma," and it has been claimed³⁵ that neoplasms of this type may behave in a relatively benign fashion. It is, however, extremely difficult to exclude, in any large solid tumor, the presence of small foci of undifferentiated or poorly differentiated cells, and this may account for the experience of those⁴ who have found that even histologically innocuous solid teratomas run a highly malignant clinical course. It does appear, though, that if the only malignant constituent of an otherwise mature teratoma is neuroglial tissue, the prognosis is relatively good.²⁷

The benign cystic teratoma (dermoid) is very common but the histologic appearances may be altered by the partial or complete overgrowth of one particular tissue. This is usually accepted as the mode of development of a struma ovarii, and it is probable that some mucinous cystadenomas develop in a similar fashion by overgrowth, within a teratoma, of gastrointestinal type epithelium. This is suggested by the fact that a proportion of such tumors contain argyrophil and argentaffin cells in numbers that are otherwise only seen in the

gastrointestinal tract.¹⁴ It is not implied that all mucinous cystadenomas are teratomatous in origin; indeed, the majority contain no argentaffin or argyrophil cells and almost certainly arise from the germinal epithelium via a process of metaplasia and endocervical differentiation.

Malignant change occurs in about 1.5 percent of benign teratomas³⁸ and usually results in a squamous cell carcinoma; occasionally an adenocarcinoma may develop and rarely a malignant melanoma.⁶ Mesenchymal malignant lesions, such as a chondrosarcoma,¹⁸ can develop in benign teratomas and a small number of granulosa cell tumors have been shown to originate in ovarian "dermoids."⁵² Thyroidal adenocarcinoma may arise in a struma ovarii¹⁶ and carcinoid tumors can develop from gastrointestinal or bronchial epithelium contained in a benign teratoma.¹¹

Sex cord-mesenchymal tumors

The origin of granulosa cell tumors and thecomas from sex cord-mesenchyme is now widely accepted, although whether the sex cords themselves are of mesenchymal or epithelial origin is still debated.³² It is possible that granulosa cell tumors may also develop from atretic Graafian follicles.²⁹

The indifferent gonad of the early embryo has the potential to develop into either a testis or an ovary. This ambivalency is retained by sex cord-mesenchymal structures in the mature ovary and is shown by the development of tumors containing structures morphologically similar to testicular tissue. The tubular arrhenoblastoma is a particularly well differentiated form of this tumor and contains easily recognizable Sertoli cells.²⁴ In less well differentiated arrhenoblastomas the resemblance to testicular tissues is less apparent, but hilar cells are present in many cases and it is now clear that these are the homolog of testicular Leydig cells.²⁴ Pure hilar cell tumors also occur, but if the presence of Reinke crystalloids is insisted upon as a diagnostic criterion the number of proven cases is small.¹² The bisexual potential of ovarian sex cord mesenchyme is perhaps seen most clearly in the gynandroblastoma, which contains elements histologically resembling both arrhenoblastoma and granulosa-cell thecoma patterns.

Reported series of lipid cell tumors have often included examples of hilar cell tumors. If these are excluded, however, a well characterized neoplasm remains which, histologically, often resembles

adrenocortical tissue. An origin of this tumor from adrenal rests, although often proposed, has never been demonstrated and it has been suggested²⁰ that it is really a luteinized thecoma developing usually against a background of stromal hyperplasia. Recently, though, it has been shown⁴⁸ that lipid cell tumors usually contain an admixture of cell types, some resembling hilar cells and others adrenocortical cells. This has prompted the suggestion that the tumors are derived from medullary ovarian mesenchyme that is capable of transforming into either of these two cell types.

Germinal (coelomic) epithelial tumors

This group requires little comment, for the ability of ovarian germinal (coelomic) epithelium to undergo metaplasia into various types of Mullerian epithelium is well documented.³⁶ Ovarian endometriosis may develop in other ways but it is probable that metaplasia accounts for a proportion of cases and that, in such cases, endometriosis can be considered as a benign neoplasm.³⁶ Malignant change in ovarian endometriosis is probably not uncommon, for in recent years it has become increasingly apparent that the endometroid carcinoma is one of the commoner malignant ovarian neoplasms.²⁶ This tumor is morphologically identical with the uterine endometrial adenocarcinoma and almost certainly originates in a focus of endometriosis.⁴³

The clear cell carcinoma of the ovary was formerly thought to be of mesonephric origin and was often referred to as an "ovarian hypernephroma"; recently, however, it has been demonstrated that these tumors are simply histologic variants of endometroid adenocarcinomas.⁴² This is not surprising, for carcinomas in many areas of the body may, on occasion, show a clear cell pattern, and the supposition that tumor cells of this type are diagnostic of a renal or mesonephric type lesion is incorrect.

The rare mixed mesodermal sarcoma of the ovary is identical with that more commonly arising in the endometrium and is thought to develop in pre-existing ovarian endometriosis.¹⁰ Carcinosarcomas of the ovary are merely variants of this tumor whilst overgrowth of one particular tissue in a mixed sarcoma may give rise to such curiosities as a rhabdomyosarcoma³⁷ or osteogenic sarcoma⁴⁷ of the ovary.

Tumors of non-specialized stroma

These tumors are similar to those occurring

elsewhere in the body, although, with the exception of the fibroma, they are surprisingly uncommon. It is doubtful if a true morphologic distinction can be drawn between a thecoma and a fibroma; the constituent cells are identical at both the light and electron microscopic level⁵³ and the presence or absence of free fat has not been found to be a reliable differentiating feature.⁷

Mesonephric tumors

A mesonephric origin has been disproved for both the "Schiller mesonephroma" and the clear cell carcinoma of the ovary, whilst the evidence suggesting that the adenomatoid tumor is a mesonephric neoplasm is far from convincing.²¹ There is, however, a rare ovarian tumor for which mesonephric histogenesis appears likely. This tumor is characterized by the presence of tubular structures, cysts and eosinophilic cells set in a loose edematous stroma.⁵⁴ The contained tubular structures resemble closely the normal vasa efferentia of the male and, as these latter are derived from mesonephric tubules, it has been suggested that the ovarian mesonephroma is similarly derived.⁵⁴

Lymphoma

The ovary is not infrequently involved in disseminated malignant lymphomas,^{25,57} but it has been doubted whether primary lymphomas of the ovary exist. There have been, however, well documented cases of lymphosarcoma⁹ and Hodgkin's disease³ that were apparently confined to the ovary. Burkitt's tumor very frequently involves the ovaries, and, although this disease is seen most commonly in Africa, examples of ovarian lymphomas having a histologic appearance identical with the African cases have occurred in temperate zones.⁴⁴

Tumors of debatable histogenesis

The histogenesis of the Brenner tumor remains an enigma. The theory that this neoplasm develops from Walthard's rests fails to reconcile the disparity between the anatomic disposition of such rests and the site of Brenner tumors. Other suggestions have included an origin from germ cells, from germinal epithelium, from the rete ovarii, from follicular structures or from gonadal stroma, but perhaps the most acceptable hypothesis is that the tumor is formed of urinary tract epithelium, this arising either from mesonephric remnants or by metaplasia of the germinal epithelium.⁴⁵ Certainly, the

islands of Brenner tissue closely resemble transitional epithelium, and this is seen even more clearly in the rare malignant Brenner tumors which mimic very closely transitional cell carcinomas. The well known fact that Brenner tumors often contain mucinous columnar epithelium has been compared with the frequent occurrence of this phenomenon in the urinary tract, where it is seen in such conditions as cystitis glandularis.⁴⁵

The gonadoblastoma^{40,51} contains a mixture of germ cell and sex cord mesenchymal derivatives and characteristically is formed of mingled areas of dysgerminoma and granulosa cell tumor or arrhenoblastoma. This tumor occurs almost entirely in patients with dysgenetic gonads and this, together with the impossibility of reconciling the histologic features with an origin from a single cell type and the benign nature of the lesion, suggests that this may be a hamartoma rather than a true neoplasm.

Adenomatoid tumors, although seen more commonly in the uterus and Fallopian tubes, do occasionally occur in the ovary.^{22,55} They were originally classed as lymphangiomas or endotheliomas, but in recent years an origin from mesonephric or mesothelial tissue has been more favored.^{22,49} Perhaps the most satisfactory suggestion has been that these neoplasms are derived from Mullerian duct mesenchyme and that they are benign "Mullerian mesenchymomas."²¹ This theory explains the frequent presence of smooth muscle fibers in adenomatoid tumors, a finding that is not satisfactorily accounted for by any of the other histogenetic theories.

B. Systemic Effects of Ovarian Tumors

Endocrine effects

In the past, a clear distinction has usually been drawn between "functioning" and "non-functioning" ovarian tumors, but in recent years this distinction has become progressively blurred by the recognition that many neoplasms previously considered as functionally inert may be accompanied by evidence of either estrogen or androgen effect, more commonly the former.^{32,39} This has been particularly noted with Brenner tumors, mucinous cystadenomas, serous cystadenomas and adenocarcinomas (and is also quite common in metastatic ovarian deposits of gastrointestinal adenocarcinomas). The common factor linking these disparate neoplasms is believed to be luteinization of the tumor stroma, and there is

usually a good correlation between this morphologic change and endocrine effect.³⁹ It has been suggested that, in these tumors, the ovarian stroma undergoes luteinization because it reacts to any expanding lesion as it would to a developing follicle,¹⁹ and this has prompted the hypothesis that stromal luteinization (and hence endocrine effect) is greater in multifocal lesions, Brenner tumors, for example—because of the greater surface area presented by such tumors to the ovarian stroma.³⁹ The fact that such tumors may show either estrogen or androgen effect denotes the endocrine flexibility of the ovarian mesenchyme, and this is further reflected by the finding that tumors usually considered as feminizing may, on occasion, have a virilizing effect and vice versa.³⁹

Unusual systemic effects

Most ovarian neoplasms manifest only local symptoms but a few are accompanied by systemic clinical side effects that, whilst clearly related to the presence of the tumor, are difficult to explain. Thus, recurrent attacks of hypoglycemia have been noted in association with ovarian fibromas and fibrosarcomas,^{15,30} although analysis of these neoplasms has failed to detect any insulin-like substance. Similarly, hypercalcemia has been recorded in several cases of ovarian carcinoma,^{5,33} despite the absence of bone secondaries and without any parathyroid-like substance being isolated from the tumor. In these unusual cases the metabolic disturbance has disappeared after removal of the tumor.

A rare feature of ovarian neoplasms is the concomitant development of a hemolytic anemia that remits after removal of the tumor. The anemia is usually of the chronic type and may be either Coombs negative or positive. Nearly all the tumors complicated by a hemolytic anemia have been benign cystic teratomas²⁸ but a few have been carcinomas.⁵⁸ It has been suggested that, in the teratomas, the anemia is the result of the production of antibodies to substances within the cystic tumor, such as split proteins or unstable lipoproteins, that share a common antigen with erythrocytes.

A struma ovarii may be associated with the clinical features of thyrotoxicosis⁵⁶ and even with exophthalmos; the symptoms usually remit after removal of the ovarian tumor, for in only about a sixth of these cases is the normally situated thyroid gland also hyperplastic. It should be noted that autoimmune thyroiditis may affect ovarian thyroid

tissue and that the histologic features of Hashimoto's disease have been noted in a struma ovarii.¹³

Carcinoid tumors developing in a benign cystic teratoma may secrete serotonin and be associated with a partial "carcinoid" syndrome,¹¹ for in many of the reported cases the patients have had hot flushes together with blotchiness or discoloration of the skin; bowel disturbances have been noted in occasional cases but heart lesions have not been clinically apparent (although in one case endocardial fibrosis was noted at autopsy). No case of metastasis of an ovarian carcinoid has been recorded and this contrasts with the intestinal carcinoids, in which symptoms of the "carcinoid" syndrome only appear when metastatic deposits are present. It has been suggested that this discrepancy is due to the entry of serotonin directly into the systemic circulation via the ovarian vein in the gonadal cases without having to pass first through the portal circulation as is the case with the intestinal neoplasms.

Fibromas of the ovary are, of course, well known for their association with Meigs' syndrome, although in fact this syndrome may complicate a wide variety of benign ovarian tumors. It is of interest that ovarian fibromas may, in some cases, be an integral part of the genetically determined multiple basal cell cancer syndrome⁸ for, in a recent report of this rare disease, three of the five patients discussed had fibromas of the ovary.

REFERENCES

1. Abel, M. R., and Holtz, F.: Ovarian neoplasms in childhood and adolescence. I. Tumors of germ cell origin, *Amer. J. Obstet. Gynec.*, 92:1059-1081, 1965.
2. Arias-Bernal, L., and Jones, H. W.: Chromosomes of a malignant ovarian teratoma, *Amer. J. Obstet. Gynec.*, 100:785-789, 1968.
3. Bare, W. W., and McCloskey, J. F.: Primary Hodgkin's disease of the ovary, *Obstet. Gynec.*, 17:477-480, 1961.
4. Benirschke, K., Easterday, C., and Abramson, D.: Malignant solid teratomas of the ovary. Report of three cases, *Obstet. Gynec.*, 15:512-521, 1960.
5. Breidhal, H. D., and Ritchie, B. L.: Hypercalcaemia due to malignant ovarian tumour, *Med. J. Australia*, 49:208-210, 1962.
6. Bruning, E. G. H.: Malignant melanoma originating in a dermoid cyst of the ovary, *Amer. J. Obstet. Gynec.*, 85:131-132, 1963.
7. Burslem, R. W., Langley, F. A., and Woodcock, A. S.: A clinicopathological study of oestrogenic ovarian tumors, *Cancer*, 7:522-538, 1954.
8. Clendenning, W. E., Herdt, J. R., and Block, J. B.: Ovarian fibromas and mesenteric cysts; their association with hereditary basal cell cancer of the skin, *Amer. J. Obstet. Gynec.*, 87:1008-1012, 1963.
9. Collins, J., and Piper, P. G.: Lymphosarcoma of the ovary, *Obstet. Gynec.*, 20:686-689, 1962.
10. Czernobilsky, B., and LaBarre, G. C.: Carcinosarcoma and mixed mesodermal tumor of the ovary, *Obstet. Gynec.*, 31:21-32, 1968.
11. Doucette, J. W., and Estes, W. B.: Primary ovarian carcinoid tumors. Case report and review of the literature, *Obstet. Gynec.*, 25:94-101, 1965.
12. Dunnihoo, D. R., Grieme, D. L., and Woolf, R. B.: Hilus cell tumors of the ovary, *Obstet. Gynec.*, 27:703-713, 1966.
13. Erez, S. E., Richart, R. M., and Shertles, L. B.: Hashimoto's disease in a benign cystic teratoma of the ovary, *Amer. J. Obstet. Gynec.*, 92:273-274, 1965.

14. Fox, H., Kazzaz, B., and Langley, F. A.: Argentaffin and argyrophil cells in the normal human female genital tract and in ovarian mucinous cysts, *J. Path. Bact.*, 88:479-488, 1964.
15. Friend, J. A. R., and Hales, C. N.: Spontaneous hypoglycaemia and sarcoma, *Acta Endocr. (Kobenhavn)*, 50:233-238, 1965.
16. Gonzales-Angulo, A., Kaufman, R. H., Braungardt, C. D., Chapman, F. C., and Hinshaw, A. J.: Adenocarcinoma of thyroid rising in struma ovarii (Malignant struma ovarii), *Obstet. Gynec.*, 21:567-576, 1963.
17. Hawkins, D. F., and Lawrence, D. M.: Virilizing ovarian hilus cell hyperplasia with special reference to hormone excretion, *J. Obstet. Gynaec. Brit. Comm.*, 72:285-291, 1965.
18. Heath, L. P.: Chronodiosarcoma of the ovary arising in dermoid cyst, *Harper Hosp. Bull.*, 25:169-173, 1967.
19. Hughesdon, P. E.: Thecal and allied reactions in epithelial ovarian tumors, *J. Obstet. Gynaec. Brit. Comm.*, 65:702-709, 1958.
20. Hughesdon, P. E.: Ovarian lipoid and theca cell tumors: their origins and interrelations, *Obstet. Gynec. Survey*, 21:245-288, 1966.
21. Jackson, J. R.: The histogenesis of the "adenomatoid" tumor of the genital tract, *Cancer*, 11:337-350, 1958.
22. Jones, E. G., and Donovan, A. J.: Adenomatoid tumor of the ovary versus mesothelial reaction, *Amer. J. Obstet. Gynec.*, 92:694-698, 1965.
23. Krause, D. E., and Stenbridge, V. A.: Luteomas of pregnancy, *Amer. J. Obstet. Gynec.*, 95:192-206, 1966.
24. Langley, F. A.: "Sertoli" and "Leydig" cells in relation to ovarian tumors, *J. Clin. Path.*, 7:10-17, 1954.
25. Lathrop, J. C.: Malignant pelvic lymphoma, *Obstet. Gynec.*, 30:137, 1967.
26. Long, M. E., and Taylor, H. C.: Endometroid carcinoma of the ovary, *Amer. J. Obstet. Gynec.*, 90:936-950, 1964.
27. Malkasian, G. D., Symmonds, R. E., and Docherty, M. B.: Malignant ovarian teratomas, *Obstet. Gynec.*, 25:810-814, 1965.
28. McAndrew, G. M.: Haemolytic anaemia associated with ovarian teratoma, *Brit. Med. J.*, 2:1307-1308, 1964.
29. McKay, D. G., Hertig, A. R., and Hickey, W. F.: The histogenesis of granulosa and theca cell tumors of the human ovary, *Obstet. Gynec.*, 1:125-136, 1953.
30. Michael, C. A.: Pelvic fibroma causing recurrent attacks of hypoglycaemia in a post-menopausal patient, *Proc. Roy. Soc. Med.*, 59:835, 1966.
31. Minkowitz, S., Friedman, F., and Henniger, G.: Xanthogranuloma of the ovary, *Arch. Path.*, 80:209-213, 1965.
32. Morris, J. M., and Scully, R. E.: Endocrine Pathology of the Ovary, C. V. Mosby Co., St. Louis, 1958.
33. Noenincux, F., Six, R., and Laethem, V.: Tumeur maligne d'ovaire a effet hypercalcemiant et phosphaturique, *Acta Clin. Belg.*, 17:406-415, 1962.
34. Norris, H. J., and Taylor, H. B.: Nodular theca-lutein hyperplasia of pregnancy (so-called "pregnancy luteoma"), *Amer. J. Clin. Path.*, 47:557-566, 1967.
35. Novack, E. R.: Solid teratomas of the ovary; with respect to five cases, *Amer. J. Obstet. Gynec.*, 56:300-310, 1948.
36. Numers, C. von: Observations on metaplastic changes in the germinal epithelium of the ovary and on the aetiology of ovarian endometriosis, *Acta Obstet. Gynec. Scand.*, 44:107-116, 1965.
37. Payan, H.: Rhabdomyosarcoma of the ovary. Report of a case, *Obstet. Gynec.*, 26:393-395, 1965.
38. Peterson, W. F.: Malignant degeneration of benign cystic teratomas of the ovary. Collective review, *Obstet. Gynec. Survey*, 12:793-830, 1957.
39. Scott, J. S., Lumsden, C. E., and Levell, M. J.: Ovarian endocrine activity in association with hormonally inactive neoplasia, *Amer. J. Obstet. Gynec.*, 97:161-170, 1967.
40. Scully, R. E.: Gonadoblastoma, *Cancer*, 6:455-463, 1953.
41. Scully, R. E.: Stromal luteoma of the ovary, *Cancer*, 17:769-778, 1964.
42. Scully, R. E., and Barlow, J. F.: Mesonephroma of ovary. Tumor of Mullerian origin related to the endometroid carcinoma, *Cancer*, 20:1405-1417, 1967.
43. Scully, R. E., Richardson, G. S., and Barlow, J. F.: The development of malignancy in endometriosis, *Clin. Obstet. Gynec.*, 9:384-411, 1966.
44. Seed, P. G.: Burkitt's tumor in Britain, *J. Obstet. Gynec. Brit. Comm.*, 73:808-811, 1966.
45. Sternberg, W. H.: Non-functioning ovarian neoplasms, *In The Ovary*, ed. H. G. Grady and D. E. Smith, Williams and Wilkins, Baltimore, 1963, p. 209.
46. Stevens, L. C.: The biology of teratomas, *In Advances in Morphogenesis*, ed. M. Abercrombie and J. Brachet, Academic Press, New York and London, 1967, Vol. 6, p. 1.
47. Stone, L. M., and Wyatt, J. Y.: Osteogenic sarcoma of the ovary, *Amer. J. Obstet. Gynec.*, 64:422, 1952.
48. Taylor, H. B., and Norris, H. J.: Lipid cell tumors of the ovary, *Cancer*, 20:1953-1962, 1967.
49. Teilum, G.: Histogenesis and classification of mesonephric tumors of the female and male genital system and relationship to benign so-called adenomatoid tumors (mesotheliomas). A comparative histological study, *Acta Path. Microbiol. Scand.*, 34:431-481, 1954.
50. Teilum, G.: Endodermal sinus tumor of the ovary and testis. Comparative morphogenesis of the so-called "Mesonephroma ovarii" (Schiller) and extraembryonic (yolk sac allantoic) structures of the rat's placenta, *Cancer*, 12:1092-1105, 1959.
51. Teter, J.: A new concept of classification of gonadal tumors arising from germ cells (gonocytoma) and their histogenesis, *Gynaecologia (Basel)*, 150:84-102, 1960.
52. Thompson, J. P., Dockerty, M. B., and Symonds, R. E.: Granulosa cell carcinoma arising in a cystic teratoma of the ovary. Report of a case, *Obstet. Gynec.*, 28:549-552, 1966.
53. Toker, C.: Theca cell tumor, *Amer. J. Obstet. Gynec.*, 100:779-784, 1968.
54. Wade-Evans, T., and Langley, F. A.: Mesonephric tumors of the female genital tract, *Cancer*, 14:711-719, 1961.
55. Williamson, H. O., and Moore, M. P.: Ovarian and para-ovarian adenomatoid tumors. Case reports, *Amer. J. Obstet. Gynec.*, 90:388-394, 1964.
56. Woodruff, J. D., and Marley, R. L.: Struma ovarii. Demonstration of both pathologic change and physiologic activity: report of four cases, *Obstet. Gynec.*, 9:707-719, 1957.
57. Woodruff, J. D., Castillo, N., and Novack, E. R.: Lymphoma of the ovary. A study of 35 cases from the ovarian tumor registry of the American Gynecological Society, *Amer. J. Obstet. Gynec.*, 85:912-918, 1963.
58. Yan, L. T., Ruzski, C., Busch, S., and Leithold, S. L.: Ovarian neoplasm associated with autoimmune hemolytic anemia, *Amer. J. Obstet. Gynec.*, 95:207-211, 1966.

CARCINOMA OF THE NASOPHARYNX IN CHINESE MEN

"In San Francisco we have a large Chinese population. We consider that any Chinese male who comes to us with a blocked ear has a carcinoma of the nasopharynx until proved otherwise. Actually, it's about 20 times as common in Cantonese-Chinese (which is the type we have) as it is in the population at large; so that in every case and certainly in the male Chinese, it is absolutely imperative to have a good look, not just a passing glance with a mirror, at the nasopharynx."

—ROBERT C. McNAUGHT, M.D., San Francisco
Audio-Digest Otorhinolaryngology, Vol. 1, No. 1

The Penicillins, Old and New

Review and Perspectives

PAUL D. HOEPRICH, M.D., *Davis*

IT IS CONVENIENT, in reviewing developments that span many years, to break the time that has passed into decadal periods. Taking Fleming's discovery of penicillin in 1928 as the point for departure,¹ 1968 becomes the year of commencement of the fifth decade of penicillin (Table 1).

Decade I

Following his original observation that staphylococci were inhibited from growth on a culture plate in the vicinity of a contaminating mold—subsequently identified as *Penicillium notatum*—Dr. Fleming prepared extracts of broth cultures of his strain of *P. notatum*. He named his crude material penicillin and observed its remarkable antibacterial activity and virtual lack of toxicity to experimental animals. Although Fleming continued to work with penicillin and write about his discovery, he attracted little interest. About the only use made of penicillin during this first decade was as an additive to culture media to facilitate isolation of *Hemophilus* sp.

Decade II

In 1938, a group of investigators, headed by Dr. Howard Florey, undertook study of penicillin at the Sir William Dunn School of Pathology at Oxford. The properties of extraordinary antibacterial potency with seeming absence of toxicity for animals, as noted by Fleming, were confirmed and extended.² Despite the exigencies of World War II, the work continued and the Oxford group de-

veloped production of penicillin to a practical level that allowed clinical trial. With proof of therapeutic efficacy, there was obvious need for mass production of penicillin—a development impossible in embattled Britain. In July, 1941, the focus of research on penicillin shifted to the Northern Regional Research Laboratory of the U.S. Department of Agriculture in Peoria, Illinois.

With alteration of the culture medium, selection of naturally occurring variants, application of mutagens with further selection, the yield of penicillin from *P. notatum* was brought to 150-200 units per ml from a starting level of 2 to 5 units per ml. No further improvement in yield from *P. notatum* seemed possible; moreover, since surface growth of the mold was necessary, real efficiency in production was not possible. Deep tank, submerged culture had to be employed for reduction in production costs but *P. notatum* made very little penicillin when grown submerged in liquid media.

Screening of isolates of *Penicillium* sp. from soil samples collected from all over the world failed to turn up a variant that would grow submerged and make penicillin. However, in 1944 a strain of *Penicillium chrysogenum* isolated from a moldy cantaloupe found in a produce market in Peoria was found to produce around 260 units per ml growing in submerged culture. Irradiation and exposure to radiomimetic chemicals, with selection, led to the presently used descendants of the Peoria cantaloupe strain of *P. chrysogenum* that yield over 3,000 units per ml of culture medium.

There was a notable perturbation in 1945 soon after a high-yield mutant was put into production of penicillin. The penicillin that was produced was measured in units of potency by conventional in

From the Section of Clinical Microbiology and Immunology, Department of Internal Medicine, School of Medicine, University of California, Davis and the Sacramento County Hospital, Sacramento.

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Reprint requests to: Section of Clinical Microbiology and Immunology, Department of Internal Medicine, School of Medicine, University of California, Davis 95616.

TABLE 1.—The year 1968 is the beginning of the fifth decade since Fleming's discovery of penicillin

Decade	Event	Application
I 1928-1938	Discovery	Additive to culture media
II 1938-1948	Development	Production Purification Therapeutic application
III 1948-1958	Directed biosynthesis	Recognition and preparation of discrete penicillins: acid resistant penicillinase resistant altered spectrum
IV 1958-1968	Chemical synthesis and semi-synthesis	
V 1968-	? Design and preparation of penicillins with a limited range of antimicrobial activity	

vitro assay. But when it was used to treat infections the mutant-produced penicillin was less effective, unit for unit, than the parent-mold penicillin. It was soon found that the difficulty related to the fact that there was not a penicillin, but, in fact, penicillins. The new mutant made principally penicillin K (n-heptylpenicillin), a penicillin even more active in the test tube than penicillin G (benzylpenicillin). However, when given in therapy, penicillin K apparently entered into such firm binding with proteins of the host that it was unavailable for antibacterial action. The situation improved dramatically when it was discovered that high yield could be maintained, but deviated to the production of penicillin G by supplying phenylacetic acid in the culture medium. Such directed biosynthesis of penicillin G was possible because the final step in the biosynthesis of any penicillin is acylation—the addition of an organic acid to the primary amino group of the nucleus that is characteristic of all penicillins (Chart 1).

Decade III

It was a short step to trial of other organic acids, not known to be components of natural penicillins. In this way, biosynthesis was directed to yield penicillin V (phenoxymethylpenicillin), by addition of phenoxyacetic acid to the culture medium. The first penicillin that was resistant to degradation by acid was the result and reliable peroral therapy with a penicillin was the consequence.

Another example of directed biosynthesis was penicillin O (allylthiomethylpenicillin). Heralded as a kind of penicillin which would be safe for use in patients with demonstrated hypersensitivity to penicillin G, penicillin O is of historical interest.

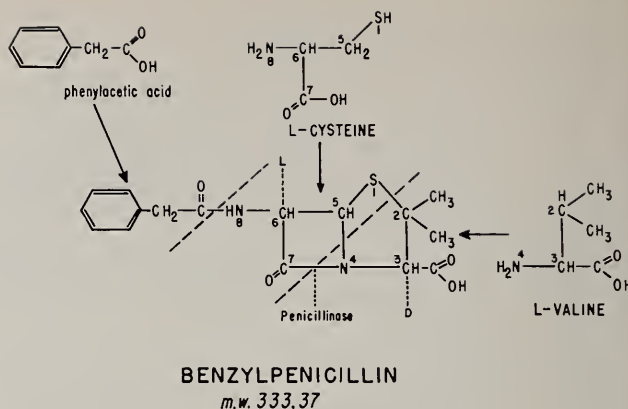


Chart 1.—The biosynthesis of 6-aminopenicillanic acid, the bicyclic dipeptide nucleus common to all penicillins, results from condensation of L-cysteine with L-valine. Note that inversion of the optical activity of carbon atom 3 (valine) results on condensation. Acylation with phenylacetic acid completes the synthesis of benzylpenicillin.

Since penicillin O also engendered hypersensitivity reactions, it became clear that alteration in the side-chain that differentiates one penicillin from another does not alter the allergenic nature of the molecule.

The biosynthetic origins of the basic penicillin nucleus were deciphered in 1957.³ As is shown in Chart 1, 6-aminopenicillanic acid, the bicyclic dipeptide that is the penicillin nucleus, is made from the amino acids L-cysteine and L-valine. Curiously, the optically active carbon atom of the L-valine precursor is inverted during condensation—a fact of enormous importance to chemical synthesis of penicillins.

Decade IV

In 1959, Sheehan and Henery-Logan reported the total synthesis of penicillin V.⁴ In the course of laboratory synthesis, all possible stereoisomers of penicillin V were produced. It was proved beyond doubt that the centers of optical activity in the 6-aminopenicillanic acid nucleus had to be precisely the way the *Penicillium* mold oriented these carbon atoms during the biosynthesis of penicillins in nature. It became apparent then, as a result of the total synthesis of penicillin, that the only part of the penicillin molecule which was susceptible to alteration was the side chain. Two other events occurred at about this same time that also had bearing on semi-synthesis.

Batchelor, in Great Britain, isolated a variant of *Penicillium chrysogenum*, which, in a special culture medium, synthesized 6-aminopenicillanic acid without any side chain attached to it.⁵ One year

TABLE 2.—Comparison of Penicillins

Penicillin	Resistance to				Potency				Versus			
	Penicillinase		Acid		<i>Staphylococcus aureus</i>				<i>Strep. pyogenes</i> Group A		<i>S. typhi</i>	
					Pcn'ase +	Pcn'ase —						
Benzyl (G)	Low	10	Low	5	Low	0	High	100	High	100	Low	25
Phenoxymethyl (V)	Low	10	Mod.	60	Low	0	High	100	High	100	Low	10
Methicillin*	High	100	Low	0.3	Mod.	25	Low	5	Low	5	Low	0
Oxacillin†	High	80	Mod.	60	High	100	Mod.	50	Low	15	Low	5
Nafcillin†	High	80	Mod.	60	High	100	Mod.	50	High	80	Low	5
Cloxacillin†	High	80	Mod.	60	High	100	Mod.	50	High	80	Low	5
Dicloxacillin†	High	80	Mod.	60	High	100	Mod.	50	High	80	Low	5
Ampicillin	Low	10	High	100	Low	2	Low	15	Low	15	High	75

*Methicillin has no place in modern therapeutics.

†While similar in many respects, these agents do differ significantly in:

(1) Efficiency of absorption from the gastrointestinal tract: dicloxacillin > [oxacillin=cloxacillin] > nafcillin.

(2) Potency against non-staphylococcal Gram + cocci: [nafcillin=cloxacillin=dicloxacillin] > oxacillin.

(3) That is: for parenteral injection nafcillin and cloxacillin are interchangeable (do not use oxacillin); for oral administration, dicloxacillin is preferable (do not use nafcillin).

later, Sakaguchi and Murao reported the liberation of 6-aminopenicillanic acid from penicillin G by an amidase isolated from another strain of *P. chrysogenum*.⁶ The work of Sakaguchi and Murao was confirmed in other laboratories, and other fungi were found capable of elaborating acylases active against various penicillins.⁷ As a result, enormous supplies of 6-aminopenicillanic acid derived from *Penicillium* fermentation became available and the preparation of penicillins by the chemical addition of side chains—that is, semi-synthesis—was commercially feasible.

There were three major goals to semi-synthesis. Not mutually exclusive and not yet completely realized, these were the preparation of penicillins that were:

(1) Resistant to inactivation by β -lactamases, for example the penicillinase of *Staphylococcus aureus*;

(2) Resistant to degradation by acid;

(3) Significantly altered in antibacterial spectrum from penicillin G. The present state of semi-synthetic penicillins will be considered according to these goals.

β -lactamase resistance

Methicillin, the first semi-synthetic, penicillinase-resistant penicillin, remains the most resistant penicillin to inactivation by β -lactamases thus far prepared. However, other deficiencies are so great as to relegate methicillin to the dustbin of history (see Table 2). Not only are oxacillin, nafcillin, cloxacillin and dicloxacillin resistant to β -lactamases, but also, these semi-synthetic penicillins resist degradation by acid and are measurably more active antimicrobics. Dicloxacillin is the most efficiently absorbed of the penicillinase-re-

sistant penicillins and so is preferable for peroral treatment of infections caused by penicillinase-producing *Staphylococcus aureus* that are not life-threatening. Life-threatening infections caused by penicillinase-producing *S. aureus* are indication for parenteral therapy. Nafcillin and cloxacillin are interchangeable and are preferable, for both are measurably more active than oxacillin and methicillin, the only other semi-synthetic, penicillinase-resistant penicillins at present available for parenteral administration. Ampicillin is of no value in the treatment of staphylococcal infections. The penicillinase-resistant penicillins have but one indication—infection caused by penicillinase-producing *S. aureus*.

Acid resistance

The variation in acid-lability among penicillins is great, ranging from the extreme in lability with methicillin to the extreme in stability with ampicillin (Table 2). While relative stability to acid will insure that active drug will pass into the duodenum after peroral administration, efficient absorption is not thereby guaranteed. For example, although ampicillin is the most resistant of available penicillins to degradation by acid, only 15 to 20 percent of a peroral dose attains to systemic distribution—see Chart 2. Although ampicillin is susceptible to inactivation by β -lactamases elaborated by enteric bacteria, it is probable that the apparently poor absorption that occurs is consequent on enterohepatic cycling. There is efficient hepatic removal of ampicillin from portal blood with excretion in the bile followed by reabsorption from the gut.¹¹ This is a phenomenon of clinical significance. For illustration:

A 52-year-old white man was admit-

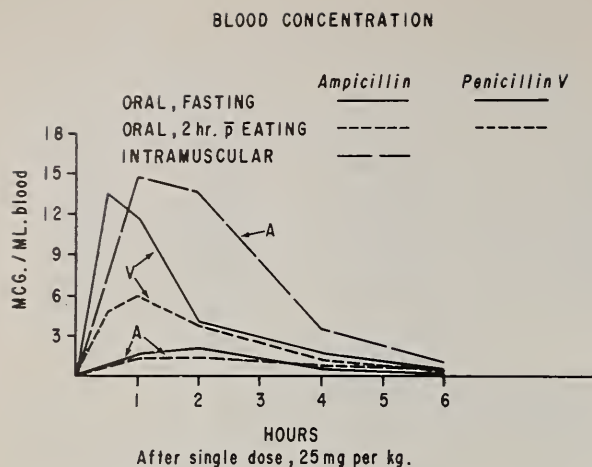


Chart 2.—As judged by penicillinemia, only 15 to 20 percent of a peroral dose of ampicillin attains to blood-borne systemic distribution.⁸ Data regarding the same dosage of penicillin V are shown for comparison.^{9,10}

ted for resection of a carcinoma of the greater curvature of the stomach that had been diagnosed at another hospital. At operation an 80 percent gastrectomy, omentectomy and splenectomy were performed to remove a large, ulcerated gastric carcinoma. The patient became febrile almost immediately after operation. Four days later a left subdiaphragmatic abscess was diagnosed and drained at operation the following day. After drainage, the patient was treated with cephalothin, 6 gm, intravenously, daily. Fever, averaging 102.5°F, persisted. On the fourth day after drainage, because the *Escherichia coli* isolated from the pus was susceptible to ampicillin, cephalothin was stopped and ampicillin, 0.5 gm by mouth every six hours, was started. Fever, toxicity, and copious drainage of pus persisted during the next four days. Oral therapy was then replaced by intramuscular injection of 2.0 gm of ampicillin every six hours. The temperature fell to normal in 24 hours; gradual return of well-being and decrement in drainage followed over several days. Oral candidiasis, symptomatic since the seventh postoperative day, responded to gargling with mystatin mouth wash.

Altered spectrum

Among Gram-positive cocci, the enterococcal group of streptococci are notably resistant to benzylpenicillin. The standard treatment, a combination of benzylpenicillin and streptomycin, is often effective. However, there are disadvantages to the administration of two drugs, and the combination is not uniformly effective. By *in vitro*

testing, the bactericidal potency of ampicillin against enterococci is significantly greater than that of benzylpenicillin.^{12,13} There may be clinical reflection of these facts:

A 63-year-old white man was referred because of bacterial endocarditis caused by *Streptococcus fecalis*, consequent on transurethral resection of the prostate five months earlier. Because of a history of allergic sensitivity to penicillin, initial therapy at another hospital included various non-penicillin antibiotics, and cephalothin, in large doses. There was defervescence, but persistence of malaise, increasing confusion and disorientation. In addition, blood cultures obtained while the patient was receiving cephalothin and chloramphenicol, the regimen of antimicrobics that was being given at the time of referral, yielded *S. fecalis*. There was also failure of bactericidal action against the *S. fecalis* isolated from the patient by undiluted serum obtained from the patient during treatment.

On admission, the confused, quasi-oriented, rather wasted patient had, also, a holosystolic apical murmur radiating to the axilla, mild anemia, and an elevated sedimentation rate. Blood cultures yielded *S. fecalis*.

Ampicillin was bactericidal by *in vitro* test, at 0.01 μ Gm per ml, while penicillin G and cephalothin had no bactericidal activity. Intradermal and intramuscular tests with ampicillin yielded no reaction. Accordingly, treatment was started with ampicillin, 10 gm daily by continuous intravenous infusion. At this dose, however, the patient's serum did not show bactericidal activity against *S. fecalis*. Ampicillin was increased to 20 gm daily; in addition, probenecid 2.0 gm a day by mouth, and vancomycin 2.0 gm a day, intravenously, were given. On this regimen, the bactericidal activity demonstrable at a 1:2 dilution of the patient's serum could be abolished by addition of penicillinase.

He was treated for six weeks and was well and active when last observed, a year and a half after treatment.

While *Listeria monocytogenes* are susceptible to ampicillin by *in vitro* testing, benzylpenicillin is significantly more active.¹⁴ Trial of ampicillin in the treatment of listeriosis has been too meager to permit evaluation.

Significant change in antibacterial spectrum, as compared with benzylpenicillin, has been claimed for ampicillin with regard to the Gram-negative bacilli *Hemophilus influenzae*, *Escherichia coli*,

TABLE 3.—Comparison of the susceptibility of isolates of *Hemophilus influenzae* from the cerebrospinal fluid^{17,18}

Authors, date	$\mu\text{Gm. per ml. of}$	
	Benzylpenicillin	Ampicillin
Ivler <i>et al.</i> , 1963	0.10-1.6* 126 isolates	0.10-1.6* 126 isolates
Barnett <i>et al.</i> , 1966	0.20-1.56† 15 isolates	0.025-0.78† 41 isolates

* Minimal bactericidal concentrations.

† Minimal inhibitory concentrations.

Salmonella sp., *Shigella* sp. and *Proteus mirabilis*. These claims will be examined in the order listed.

Hemophilus influenzae. By *in vitro* testing of the susceptibility of isolates from the cerebrospinal fluid, there was no difference in the bactericidal potency of benzylpenicillin and ampicillin (see Table 3). The treatment of meningitis caused by *H. influenzae* has been evaluated in three controlled studies that permit comparison of ampicillin as the sole antimicrobial with chloramphenicol given alone or with a sulfonamide and/or benzylpenicillin.¹⁶⁻¹⁸ It is clear that ampicillin alone, given by intravenous injection in a dose of 150 to 400 mg per kg of body weight per day, is quite as effective as multi-agent therapy (Table 4).

In view of the identity in bactericidal potency of benzylpenicillin and ampicillin by *in vitro* test, it is curious that success with benzylpenicillin comparable to that obtained with ampicillin has not been reported. Very likely the difficulty is no more than inadequacy of dosage with benzylpenicillin. For example, Zinnemann in 1946¹⁹ probably gave as much as 2 to 20 mg of benzylpenicillin per kg of body weight per day by intramuscular injection, along with 6 to 38 mg injected into the lumbar subarachnoid space. Supporting the notion of inadequate dosage is the report of Howe²⁰ describing inadvertent cure of meningitis caused by *H. influenzae* but treated with benzylpenicillin (12 to 135 mg per kg body weight per day by intramuscular injection) under the mistaken diagnosis of meningococcal meningitis.

Escherichia coli. About 80 percent of clinical isolates of *E. coli* are inhibited from growth *in vitro* by concentrations of ampicillin that are relevant to therapy²¹⁻²³—a situation matched by benzylpenicillin.²³ Urinary tract infections caused by *E. coli* can usually be successfully treated with either kind of penicillin^{22,24,25} because these infections are usually infra-nephric and penicillins are concentrated in the urine as a consequence of excretion.

Life-threatening infections with *E. coli* are best treated with another antimicrobial agent that has greater probability of bactericidal effectiveness unless there is certainty that the *E. coli* causing the infection is killed *in vitro* by 25 μGm (or less) ampicillin per ml. The following report is illustrative:

A 77-year-old white woman was admitted with pneumonia. She had a history of repeated pulmonary infections and severe rheumatoid arthritis. Initial therapy with penicillin G, directed against the staphylococcus isolated from the sputum, was associated with clinical improvement. However, two weeks after admission, after penicillin had been discontinued for several days, an x-ray film of the chest showed a new infiltrate. Transtracheal aspiration of lower respiratory tract secretions yielded large numbers of *Hemophilus influenzae*. Ampicillin therapy, 1 gm, intramuscularly every eight hours, was begun. Despite clinical and radiologic evidence of improvement of the pulmonary infection, the patient remained mildly febrile. Blood and urine cultures were sterile. On the fifteenth day of ampicillin therapy, the temperature suddenly rose to 105°F; hypotension intervened and the patient died. Blood and sputum cultures taken premortem yielded *Escherichia coli*.

Salmonella sp. According to *in vitro* study, both typhoidal and non-typhoidal species of *Salmonella* are susceptible to ampicillin.²⁶⁻²⁸ Indeed, in the test tube, ampicillin is more active than

TABLE 4.—Ampicillin employed alone in the treatment of meningitis caused by *Hemophilus influenzae* was at least as effective as multi-agent regimens¹⁶⁻¹⁸

Authors, date (dosage)	Mortality	Sequelae
Mathies <i>et al.</i> , 1965 (150 mg./kg./day)	4/66 = 6.1%* (10/107 = 9.3%)†	6/66 = 9.0%* (11/107 = 10.2%)†
Barrett <i>et al.</i> , 1966 (150 mg./kg./day)	1/16 = 3.5%* (2/12 = 16.7%)†	4/16 = 25%* (5/12 = 41.7%)†
Fleming <i>et al.</i> , 1967 (400 mg./kg./day)	1/21 = 4.8%* (1/20 = 5.0%)†	?

* Ampicillin therapy.

† Chloramphenicol, 100 mg per kg body weight per day by intravenous injection, with or without sulfonamide and/or benzylpenicillin, for one day.

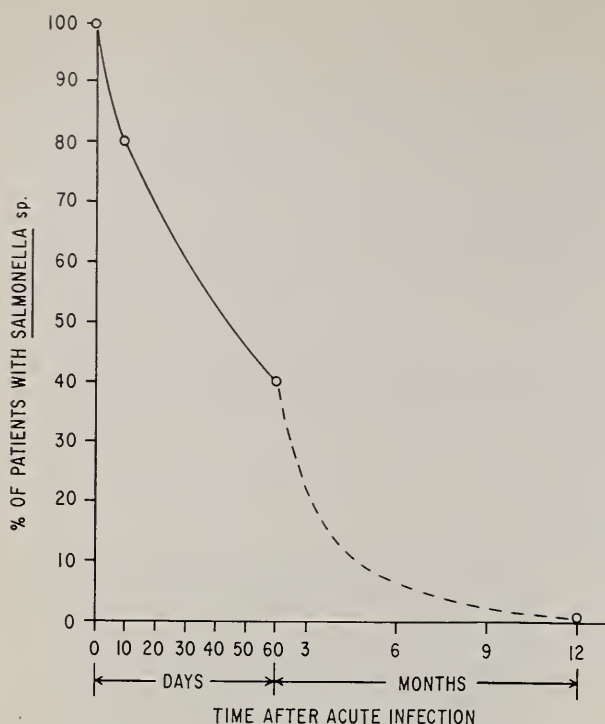


Chart 3.—Following subsidence of acute clinical illness, there is spontaneous cessation of excretion of the infecting *Salmonella* sp. in an essentially exponential decline with time. True carriers, those who continue shedding one year after acute disease, range from 2 to 5 percent with *Salmonella typhi* to less than 1 percent with non-typhoidal *Salmonella* sp.

either benzylpenicillin or chloramphenicol against *Salmonella typhi*. In addition, the pharmacologic property of excretion by the liver with actual concentration in the bile led to speculation that ampicillin might have particular merit in dealing with carriers of *Salmonella* sp.

There is now sufficient experience to indicate that peroral therapy with ampicillin is inferior to peroral therapy with chloramphenicol in the treatment of both acute typhoid fever and non-typhoidal salmonellosis.^{8,28-37} In one clinical trial, ampicillin given by injection (ten patients) was as effective as chloramphenicol given by injection (ten patients) in treatment of typhoid fever.³⁸ However, in another study, none of five patients with non-typhoidal salmonellosis were cured by parenteral administration of ampicillin.³⁹

Following subsidence of acute salmonellosis, there is natural, spontaneous cessation of excretion of bacilli according to a pattern approximating exponential decay (Chart 3). For this reason, valid evaluation of the effect of any regimen of treatment of carriers of *Salmonella* sp. must refer to true carriers—those who continue to shed *Sal-*

monella sp. one year after clinical recovery from acute salmonellosis. The incidence of true carriers following typhoid fever is 2 percent to 5 percent; following non-typhoidal salmonellosis, less than 1 percent. The presence of biliary tract disease, with or without cholelithiasis, is conducive to the establishment of a carrier state. However, persons who appear to have normal biliary tracts may become true carriers. Chloramphenicol has not been effective in the treatment of true carriers of *Salmonella* sp.

Since the only known host to *S. typhi* is the human, many investigators have assessed the utility of ampicillin to the treatment of the true typhoid carrier. Referring only to those reports dealing with three or more true carriers, treatment with ampicillin was apparently successful with 49 of 79 patients.⁴⁰⁻⁴⁹ On the whole, the probability of success was enhanced if there was no biliary disease, or if a diseased gallbladder was removed. High dosage, 4 to 6 gm per day for four to six weeks, supplemented with probenecid, 2 gm per day, also made for success in terminating carriage of *S. typhi*.

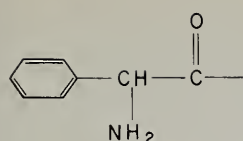
Carriers of non-typhoidal *Salmonella* sp. have been less well studied. However, reports of 14 carriers treated with ampicillin tell of but two cures.^{37,39,40-42,46,48}

Shigella sp. With increasing frequency clinical isolates of *Shigella* sp. are resistant to the sulfonamides as well as to other antimicrobial agents. Therefore it is of clinical significance that the effectiveness of ampicillin in the treatment of bacillary dysentery has been documented.^{8,50,51}

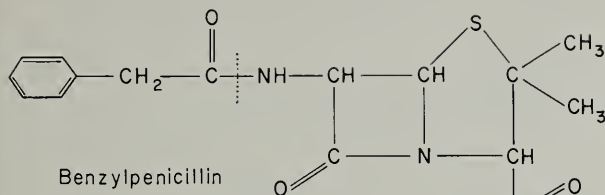
Proteus mirabilis. Of the *Proteus* sp., only *P. mirabilis* is susceptible to ampicillin. The degree of susceptibility to ampicillin is not remarkably greater than that displayed to benzylpenicillin.⁵² Since high dosage parenteral therapy is required with either kind of penicillin (8 to 25 gm per day) for successful treatment of renal or extra-renal infections caused by *P. mirabilis*, cost alone dictates preference for benzylpenicillin.

Decade V

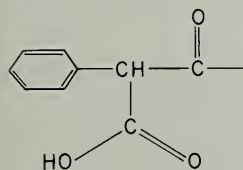
What of the future of penicillins? Surely the reagent shelves of the chemists are not yet bare insofar as side-chain variation is concerned. However, with the logging of more than 2,000 semi-synthetic penicillins, differing only in side-chain structure,⁵³ it might seem that the probability of preparation of additional useful penicillins through



Ampicillin



Benzylpenicillin



Carbenicillin

Chart 4.—Carbenicillin, the newest of the semi-synthetic penicillins to come to clinical investigation, like ampicillin, is a variant of benzylpenicillin. However, carbenicillin and ampicillin are antipodean variants for the carboxyl grouping of the former is electronegative whereas the primary amino grouping of the latter is electropositive.

acylation is becoming remote. Yet, the recent reports of effectiveness against *Pseudomonas aeruginosa* of the semi-synthetic penicillin, carbenicillin^{54,55} may indicate that there is more to come. In structure, carbenicillin is as radically deviant from ampicillin as it can be (see Chart 4), for the primary amino grouping of the ampicillin side chain is replaced with a carboxyl group. The trend in semi-synthesis that may be illustrated by carbenicillin is to penicillins with a narrow range of effectiveness—penicillins selected to deal with relatively specific, problem groups of bacteria. Carbenicillin is nicely illustrative for it promises to be useful against *Pseudomonas* sp., *Providencia* sp. and perhaps the indole positive *Proteus* sp.^{55,56}

Conclusion

There is no more dramatic story than that of the penicillins, for no other event has so profoundly and irrevocably changed clinical medicine. In tracing the path from discovery to the present, recent developments have been weighted, since this is the area of penicillin yet in the flux of in-

vestigation. The story is not yet ended and a direction that might be followed in the fifth decade of penicillin has been indicated.

REFERENCES

1. Fleming, A.: On the antibacterial action of cultures of a penicillium with special reference to their use in the isolation of *B. influenza*, *Brit. J. Exp. Path.*, 10:226-236, 1929.
2. Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G.: Penicillin as a chemotherapeutic agent, *Lancet*, 2:226-288, 1940.
3. Arnstein, H. R. V.: The biosynthesis of penicillin and some other antibiotics, *Ann. Report Chem. Soc. (London)*, 54:339-352, 1957.
4. Sheehan, J. C., and Henery-Logan, K. R.: The total synthesis of penicillin V, *J. Am. Chem. Soc.*, 79:1262-1263, 1957.
5. Batchelor, F. R., Doyle, F. P., Nayler, J. H. C., and Robinson, G. N.: Synthesis of penicillin: 6-aminopenicillanic acid in penicillin fermentations, *Nature*, 183:257-258, 1959.
6. Sakaguchi, K., and Murao, S.: A new enzyme, penicillin-amidase—Preliminaries, *J. Agr. Chem. Soc. (Japan)*, 23:411, 1950.
7. Hamilton-Miller, J. M. T.: Penicillinacylase, *Bact. Rev.*, 30:761-771, 1966.
8. Ross, S., Lovrien, E. W., Zaremba, E. A., Bourgeois, L., and Paig, J. R.: Alpha-amino-benzylpenicillin—A new broad spectrum antibiotic—Preliminary clinical and laboratory observation, *JAMA*, 182:238-242, 1962.
9. Cronk, G. A., Wheatley, W. B., Fellers, G. F., and Albright, H.: The relationship of food intake to the absorption of potassium alaphenoxyethyl penicillin and potassium phenoxymethyl penicillin from the gastrointestinal tract, *Am. J. Med. Sci.*, 240:219-225, 1960.
10. Griffith, R. S.: Comparison of antibiotic activity in sera after the administration of three different penicillins, *Antibiotic Med. and Clin. Ther.*, 7:129-135, 1960.
11. Stewart, G. T., and Harrison, P. M.: Excretion and re-excretion of a broad-spectrum penicillin in bile, *Brit. J. Pharm.*, 17:414-419, 1961.
12. Simon, H. J.: Antimicrobial susceptibility of Group D hemolytic streptococci (enterococci), *Am. J. Med. Sci.*, 253:14-18, 1967.
13. Sonne, M., and Jawetz, E.: Comparison of the action of ampicillin and benzylpenicillin on enterococci in vitro, *Appl. Microbiol.*, 16:645-648, 1968.
14. Nelson, J. D., Shelton, S., and Parks, D.: Antibiotic susceptibility of *Listeria monocytogenes* and treatment of neonatal listeriosis with ampicillin, *Acta Paed. Scand.*, 56:151-158, 1967.
15. Ivler, D., Thrupp, L. D., Leedom, J. M., Wehrle, P. F., and Portnoy, B.: Ampicillin in the treatment of acute bacterial meningitis, *In Antimicrobial Agents and Chemotherapy—1965*, Am. Soc. Microbiol., Ann Arbor, Mich., 1964, pp. 335-345.
16. Barrett, F. F., Eardley, W. A., Yow, M. D., and Leverett, H. A.: Ampicillin in the treatment of acute suppurative meningitis, *J. Pediatr.*, 69:343-353, 1966.
17. Mathies, A. W., Jr., Leedom, J. M., Thrupp, L. D., Ivler, D., Portnoy, B., and Wehrle, P. F.: Experience with ampicillin in bacterial meningitis, *In Antimicrobial Agents and Chemotherapy—1965*, Am. Soc. Microbiol., Ann Arbor, Mich., 1966, pp. 610-617.
18. Fleming, P. C., Murray, J. D. M., Fujiwara, M. W., Prichard, J. S., and McNaughton, G. A.: Ampicillin in the treatment of bacterial meningitis, *In Antimicrobial Agents and Chemotherapy—1966*, Am. Soc. Microbiol., Ann Arbor, Mich., 1967, pp. 47-52.
19. Zinnemann, K.: Survey of the outcome of 20 cases of *H. influenzae* meningitis related to bacterial type, *Brit. Med. J.*, 2:931-936, 1946.
20. Howe, C.: *Hemophilus influenzae* meningitis—Report of two cases in adults, *Ann. Int. Med. J.*, 47:141-145, 1957.
21. Rolinson, G. N., and Stevens, S.: Microbiological studies on a new broad spectrum penicillin, "Penbritin," *Brit. Med. J.*, 2:191-196, 1961.
22. Anderson, K. N., Kennedy, R. P., Florde, J. J., Shulman, J. A., and Petersdorf, R. G.: Effectiveness of ampicillin against gram-negative bacteria, *JAMA*, 187:555-561, 1964.
23. Hoeprich, P. D., Watanabe, F., and Parker, R. H.: Grouping of Gram negative bacteria and susceptibility to antimicrobial agents, *In Antimicrobial Agents and Chemotherapy—1965*, Am. Soc. Microbiol., Ann Arbor, Mich., 1966, pp. 412-416.
24. Brumfitt, W., Percival, A., and Carter, M. J.: Treatment of urinary tract infections with ampicillin—A clinical trial, *Lancet*, 1:130-133, 1962.
25. Stamey, T. A., Govan, D. E., and Palmer, J. M.: The localization and treatment of urinary tract infections—The role of bactericidal urine levels as opposed to serum levels, *Medicine*, 44:1-36, 1965.
26. Kaye, D., Merselis, J. G., and Hook, E. W.: Susceptibility of *Salmonella* species to four antibiotics, *New Eng. J. Med.*, 269:1084-1086, 1963.
27. Parker, R. H., Watanabe, F., and Hoeprich, P. D.: Susceptibility of *Salmonella heidelberg* isolated during the Utah epidemic of 1964, *In Antimicrobial Agents and Chemotherapy—1964*, Am. Soc. Microbiol., Ann Arbor, Mich., 1965, pp. 423-432.

28. Robertson, R. P., Wahab, M. F. A., and Raasch, F. O.: Evaluation of chloramphenicol and ampicillin in salmonella enteric fever, *New Eng. J. Med.*, 278:171-176, 1968.
29. Kennedy, W. P. U., Wallace, A. T., and Murdoch, J. M.: Ampicillin treatment of certain gram-negative bacterial infections, *Brit. Med. J.*, 2:962-965, 1963.
30. Patel, K. M.: Ampicillin in typhoid fever, *Brit. Med. J.*, 1:907, 1964.
31. Uwaydah, M., and Shamma'a, M.: The treatment of typhoid fever with ampicillin, *Lancet*, 1:1242-1243, 1964.
32. Scioli, C., Giusti, G., and Balestrieri, G.: Comparison of ampicillin and chloramphenicol in treatment of typhoid fever, *Postgrad. Med., Suppl.*, 40:87-91, 1964.
33. Manriquez, L., Salcedo, M., Borgono, J. M., Marzullo, E., Kraljevic, R., Parades, L., and Valdivieso, R.: Clinical trials with ampicillin in typhoid fever and paratyphoid A, *Brit. Med. J.*, 2:152-153, 1965.
34. Sanders, W. L.: Treatment of typhoid fever—a comparative trial of ampicillin and chloramphenicol, *Brit. Med. J.*, 2:1226-1227, 1965.
35. Dawkins, A. T., Jr., and Hornick, R. B.: Evaluation of antibiotics in a typhoid model, *in* *Antimicrobial Agents and Chemotherapy—1966*, Am. Soc. Microbiol., Ann Arbor, Mich., 1967, pp. 6-10.
36. Sleet, R. A., and Sangster, G.: Comparison of ampicillin and chloramphenicol in treatment of paratyphoid fever, *Brit. Med. J.*, 1:148-150, 1964.
37. Pettersson, T., Klemola, E., and Wager, O.: Treatment of acute cases of Salmonella infection and Salmonella carriers with ampicillin and neomycin, *Acta Med. Scand.*, 175:187-190, 1964.
38. Kaye, D., Rocha, H., Eyckmans, L., Pratal, A., and Hook, E. W.: Comparison of parenteral ampicillin and parenteral chloramphenicol in the treatment of typhoid fever, *Ann. N. Y. Acad. Sci.*, 145:423-428, 1967.
39. Parker, R. H., and Hoeprich, P. D.: Parenteral sodium ampicillin therapy of endocarditis, salmonellosis, and other bacterial infections, *in* *Antimicrobial Agents and Chemotherapy—1965*, Am. Soc. Microbiol., Ann Arbor, Mich., 1966, pp. 618-626.
40. Tynes, B. S., and Utz, J. P.: Factors influencing cure of salmonella carriers, *Ann. Int. Med.*, 57:871-882, 1962.
41. Bullock, W.: Ampicillin therapy of salmonella carriers—a summary of laboratory and clinical observations, *Am. J. Med. Sci.*, 246:42-47, 1963.
42. Münnich, D., Uri, J., and Valu, G.: Das kombinierte langfristig-hochdosierte Ampicillin- und Probenecid-Behandlung der Typhus-Bakterien-Dauerausscheider, *Chemother.*, 8:226-240, 1964.
43. Christie, A. B.: Treatment of typhoid carriers with ampicillin, *Brit. Med. J.*, 1:1609-1611, 1964.
44. Whitby, J. M. F.: Ampicillin in treatment of *Salmonella typhi* carriers, *Lancet*, 2:71-72, 1964.
45. Troy, P.: Ampicillin for typhoid carriers, *Brit. Med. J.*, 1:1252-1253, 1964.
46. McFadzean, A. J. S., and Ong, G. B.: Intrahepatic typhoid carriers, *Brit. Med. J.*, 1:1567-1571, 1966.
47. Simon, H., and Miller, A. C.: Ampicillin in the treatment of chronic typhoid carriers, *New Eng. J. Med.*, 274:807-815, 1966.
48. Perkins, J. C., Devetski, R. L., and Dowling, H. F.: Ampicillin in the treatment of *Salmonella* carriers, *Arch. Int. Med.*, 118:528-533, 1966.
49. Kaye, D., Merselis, J. G., Jr., Connolly, C. S., and Hook, E. W.: Treatment of chronic enteric carriers of *Salmonella typhosa* with ampicillin, *Ann. N. Y. Acad. Sci.*, 145:429-435, 1967.
50. Nelson, J. D., and Haltalin, K. C.: Broad-spectrum penicillins in enteric infections of children, *Ann. N. Y. Acad. Sci.*, 145:414-422, 1967.
51. Haltalin, K. C., Nelson, J. D., Hinton, L. V., and Kusmiesz, H. T.: Double-blind treatment study of shigellosis comparing neomycin and ampicillin, *in* *Antimicrobial Agents and Chemotherapy—1967*, Am. Soc. Microbiol., Ann Arbor, Mich., 1968, in press.
52. Barber, M., and Waterworth, P. M.: Antibiotic sensitivity of *Proteus* species, *J. Clin. Path.*, 17:69-74, 1964.
53. Sheehan, J. C.: The chemistry of synthetic and semi-synthetic penicillins, *Ann. N. Y. Acad. Sci.*, 145:216-221, 1967.
54. Acred, P., Brown, D. M., Knudsen, E. T., Rolinson, G. N., and Sutherland, R.: New semi-synthetic penicillin active against *Pseudomonas pyocyanea*, *Nature*, 215:25-30, 1967.
55. Brumfit, W., Percival, A., and Leigh, D. A.: Clinical and laboratory studies with carbenicillin—A new penicillin active against *Pseudomonas pyocyanea*, *Lancet*, 1:1289-1293, 1967.
56. Janis, B., Evans, R. G., and Hoeprich, P. D.: Providence bacillus bacteremia and septicopyemia, *Am. J. Med.*, in press.

A DOUBLE SHIBBOLETH FOR CHRONIC ACTIVE HEPATITIS

"[In diagnosing chronic active hepatitis] the laboratory tests . . . , I think, are rather . . . distinctive. And the thing that's important about the laboratory tests is that simultaneously we have evidence of chronic liver disease, largely exemplified by the serum protein changes, and at the same time, evidences of acute hepatic inflammation, largely provided by the transaminase tests. So look for evidences of chronic liver disease and acute liver disease together. In our group, unless we find both of these features in a patient, we rarely make the diagnosis of chronic active hepatitis."

—TELFER B. REYNOLDS, M.D., Los Angeles
Audio-Digest Internal Medicine, Vol. 15, No. 17

MEDICAL STAFF CONFERENCE

Heart Disease in Patients With Thyroid Dysfunction

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* As physicians we are interested in reversible and treatable forms of heart disease. We have decided to present two patients who represent two diametrically opposite kinds of endocrine dysfunction to illustrate the effect of thyroid disease on cardiac function. These two patients, who were admitted to the medical service a few months ago, illustrate quite nicely the effect of endocrine therapy on the reversal of heart disease. The first patient will be presented by Dr. Oscar Scherer.

DR. SCHERER:† The patient is a 56-year-old, Caucasian woman who entered the hospital because of chest pain and fatigue. At the age of 10 she had been admitted to San Francisco General Hospital because of what appeared to be diphtheria with cardiac involvement. At age 19 she had episodes of syncope related to both fast and slow heart rates. Because of "cardiac" complications during pregnancy at ages 32 and 35 cesarean section was carried out, and normal babies were delivered. At age 38, after her first episode of chest pain, she was told she had had a "heart attack," although she was not put into hospital and an electrocardiogram was not made. At age 40 she was given thyroid ex-

tract, 100 mg a day, although no laboratory studies were performed. In 1963 at the age of 52, left ankle and groin dissection was performed for a malignant melanosarcoma without metastasis. There has been no recurrence of this tumor. The butanol extractable iodine (BEI) was 3.0 $\mu\text{g}/100\text{ ml}$ and triodo thyroxine (T_3) uptake 13 percent at that time. One year before hospital admission the PBI and BEI were 6.0 and 4.4 μg per 100 ml respectively.

Six weeks before hospital admission she experienced increased nervousness and chest pain. At this time chest x-ray was within normal limits and thyroid medication was discontinued. One month later she was seen in the Emergency Room complaining of fatigue, cold intolerance, a weight gain of ten pounds and shortness of breath. Physical examination at that time revealed no signs of congestive heart failure or cardiac tamponade. The chest x-ray demonstrated cardiomegaly, bilateral pleural effusions and questionable pericardial effusion. Electrocardiogram showed low voltage; PBI was 1.8 μg and BEI 0.9 μg per 100 ml. The patient refused hospital admission and administration of triiodothyronine was begun, starting with 5 μg a day and increasing to 25 μg a day during the subsequent two weeks. After this two-week period of treatment

*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Oscar R. Scherer, M.D., Resident in Medicine.



Figure 1—Chest radiograph of first patient taken at time of admission to hospital.

she was admitted to hospital. An x-ray film of the chest was normal and 24-hour radioactive iodine uptake was 3 percent. After four days of treatment with thyroid stimulating hormone, radioactive iodine uptake was 2 percent.

Thyroxine was begun at 0.05 mg a day and was slowly increased to 0.125 mg a day. The most recent PBI determination was 5.8 μ g per 100 ml. X-ray films of the chest remained within normal limits. The patient continues to have atypical chest pain.

DR. SMITH: Could we see the x-ray films?

DR. YOUKER:* The first film of the chest, taken six weeks before admission to hospital, was within normal limits. A month later an increase in the cardiac size was noted (Figure 1) with a somewhat lobular configuration of the heart suggestive of pericardial effusion. There is no evidence of pulmonary vascular congestion. However, on the lateral film, blunting of both posterior costophrenic sulci is apparent and lateral decubitus films demonstrate small pleural effusions as well. A follow-up film after treatment showed a return of the cardiac silhouette to normal size and disappearance of the pleural effusions.

DR. SMITH: The patient is here for presentation. (Patient enters.) We appreciate your coming here to meet the doctors who want to hear about your problem. How are you feeling?

Patient: I have a cold.

DR. SMITH: Have you improved since you were here this summer?

Patient: Yes, my heart problem has improved.

DR. SMITH: What changes have you noticed?

Patient: Well, I can do a bit more without having a choking feeling and my strength has improved. Also I do not have to take nitroglycerin as much as I did. But I will say that I am not as good as I was last year.

DR. SOKOLOW:* Have you noticed any change in the speed with which you can do things? For instance, can you get dressed more rapidly?

Patient: Yes.

DR. SOKOLOW: Do you notice any more ease in doing things with your hands, such as sewing or using your fingers?

Patient: Not much.

DR. SMITH: She is on full thyroid replacement treatment now. Are there any other questions? Thank you very much for coming by to see us again. (Patient leaves.) The second patient will be presented by Dr. William Rutherford.

Presentation of Second Case

DR. RUTHERFORD:† The patient is a 68-year-old, white, married woman who entered the University of California Medical Center because of swelling of the feet and legs of five months' duration. The past medical history is significant in that she had an episode of rheumatic fever at age 18, requiring one year's bed rest. There was no known heart involvement with this episode. However, at age 40 she was refused government employment because of a cardiac murmur. At age 65, she was forced to retire from her usual work as a waitress because of easy fatigability. During the two years before hospital admission she had had frequent chest colds, with nonproductive cough. Seven months before hospital admission she noted dyspnea, weakness and increasing orthopnea. Five months before admission to hospital she noted peripheral edema and the gradual onset of profuse night sweats requiring two to three changes of clothing a night. Treatment with a thiazide diuretic led to improvement in the edema but had no effect on the shortness of breath.

On physical examination at the time of admission the patient appeared to be in mild respiratory distress. Blood pressure was 150/80 mm of mer-

*James E. Youker, M.D., Assistant Professor of Radiology.

*Maurice Sokolow, M.D., Professor of Medicine.

†William Rutherford, M.D., Intern in Medicine.

cury, pulse 116 per minute, respirations 24 per minute and temperature 38.2°C. The skin was fine, moist and warm, with very fine hair. The thyroid gland was full and smooth and the neck veins were distended to the cricoid cartilage at 30° elevation, with normal venous pulsation. On examination of the heart the point of maximum impulse was noted to be 1 cm medial to the anterior axillary line. There was a left ventricular thrust, and a right ventricular heave; no thrill was felt. The first heart sound was normal, the pulmonary component of the second sound was greater than the aortic component. A third sound was heard at the left sternal border. The following murmurs were heard: grade II/VI systolic at the apex with radiation to the left sternal border and axillary line; grade III/VI systolic ejection murmur at the base, radiating to the neck; grade II/VI diastolic blowing murmur at the left sternal border, and a questionable soft diastolic rumble at the apex. Scattered expiratory wheezes and rhonchi were heard throughout the chest. There were no rales. The liver edge was not felt and there was a trace of peripheral edema.

Laboratory examination: Hematocrit, 39 percent; leukocytes, 9,800 per cu mm—50 percent polymorphonuclear cells, 1 percent eosinophils, 46 percent lymphocytes and 3 percent monocytes. The sedimentation rate was 78 mm in one hour. An electrocardiogram demonstrated a sinus tachycardia with moderate left ventricular hypertrophy. BEI was 11.1 µg per 100 ml, cholesterol 137 mg per 100 ml, T₃ uptake 44 percent, and I¹³¹ uptake 20 percent at 1½ hours, 50 percent at 5 hours and 63 percent at 24 hours. A thyroid scan revealed findings consistent with a diffuse toxic goiter.

The patient was treated with 7.5 millicuries of I¹³¹ and reserpine, phenobarbital and propylthiouracil, and the cardiac symptoms abated.

DR. SMITH: The patient is here for presentation. (Patient enters.) How are you getting on now?

Patient: Pretty well.

DR. SMITH: What changes have you noticed since you were in the hospital?

Patient: Well, I can walk now without resting as frequently, and my breathing is much better.

DR. SMITH: Have you noticed any changes in sleeping, nervousness or tolerance to heat?

Patient: Everything is much better. My weight is about ten pounds less than it was.

DR. SMITH: Dr. Sokolow, would you like to mention anything?

DR. SOKOLOW: Have you noticed any change in your reaction to the weather in the last two months? When you first came here, did you have any unusual susceptibility to warm or cold weather?

Patient: I wasn't aware of any.

DR. SOKOLOW: Has anyone made any comment about your hands?

Patient: They don't shake as much.

Question from the audience: Has there been any change in the heart murmurs?

DR. SMITH: The diastolic murmur remains but is less prominent.

Thank you very much for coming. (Patient leaves.)

Here then, are two patients who have come to us in the past two months with underlying heart disease but who had superimposed complications relating to thyroid dysfunction. We have asked Dr. Maurice Sokolow to comment on the influence of thyroid dysfunction on the manifestations of heart disease.

Discussion

DR. SOKOLOW: I saw both of these patients on the same afternoon, and it struck me at the time that although there was considerable similarity between the two, in that they both had shortness of breath, nervousness and chest pain, there were striking contrasts in that one was obviously hypothyroid and the other was hyperthyroid. As Dr. Smith has said, both these conditions are potentially curable and since we now have precise techniques for determining the state of thyroid function, the physician must exclude both of these conditions in patients with heart disease. I will not discuss the laboratory or biochemical manifestations, but will confine my remarks to the clinical aspects of thyroid heart disease.

The circulatory accompaniments of the excess production of thyroid hormone produce symptoms and signs which often are confused with cardiac disease. The increased oxidative requirements of the patient who has an enormous increase in metabolic rate require that cardiac output and peripheral blood flow be increased. This increase in cardiac output and blood flow produces a combination of symptoms and signs that suggest the presence of heart disease. That is, patients may have tachycardia, peripheral vasodilatation, sweat-

ing, systolic hypertension with increased pulse pressure, a rapid upstroke of the carotid pulse, and flow murmurs in the heart. If there is underlying heart disease, then the manifestations of cardiac involvement are even more pronounced and it is difficult to separate the effect of cardiac disease from the effect of circulatory hyperactivity produced by the increased metabolic rate. There has been a good deal of controversy in the literature as to whether thyrotoxicosis can cause cardiac failure, and there are many arguments pro and con. I will elaborate as we go on.

From Sheffield, England, Sandler and Wilson,⁶ reported a study of 462 patients with thyrotoxicosis, of whom 150 had cardiac involvement. They divided the patients into those who had associated heart disease and those who did not. Although there was a large number of patients with cardiac involvement who had no obvious heart disease when they presented themselves, the majority had ischemic or hypertensive heart disease and a smaller proportion had rheumatic heart disease. Nearly half of the patients with cardiac involvement had no evidence of associated heart disease. The remaining half had underlying heart disease in which the extra load from increased cardiac output might be expected to precipitate cardiac difficulty.

Atrial Fibrillation

Sandler and Wilson showed a very striking relationship between age and the prevalence of atrial fibrillation and cardiac failure. The fact that both fibrillation and cardiac failure are uncommon below the age of 40 has been one of the strongest arguments that thyrotoxicosis does not cause heart failure. The progressive increase in the prevalence of both atrial fibrillation and congestive failure with increasing age suggests that thyrotoxicosis unmasks subclinical coronary or other degenerative heart disease but does not *per se* cause heart disease.

Atrial fibrillation is related not only to age, but also to the presence or absence of cardiac failure. As the incidence of atrial fibrillation increases, so does that of congestive heart failure. The importance of atrial fibrillation in producing dilatation and hypertrophy of the heart in cardiac failure has always been appreciated in patients with rheumatic heart disease. Levine, in particular, emphasized that atrial fibrillation, even in the absence of heart disease, and in the absence of thyrotoxicosis may lead to cardiac hypertrophy and failure. Ap-

parently the presence of atrial fibrillation is particularly serious to older patients with thyrotoxicosis.

Overlooked Thyrotoxicosis

The diagnosis of thyrotoxicosis is often overlooked in patients with atrial fibrillation and cardiac failure. The causes of this diagnostic error may be divided into three major categories.

1. The cardiac manifestations may overshadow the clinical picture of thyrotoxicosis. When the second patient under discussion today was presented to me as an example of rheumatic heart disease I was impressed by her very warm, moist hands. In addition, her movements were relatively quick for a patient with heart failure. (They were a good deal quicker than they are today.) Although she had then the symptoms of dyspnea and edema, there was a disparity between her vigor and her symptoms and signs of heart failure. It was this that led me to suspect hyperthyroidism. I think the manifestations of hyperthyroidism are usually present in these patients, but they are often overlooked because of the dominance of the cardiac symptoms.

2. Some patients present with a clinical picture referred to as "apathetic thyrotoxicosis." When the patient really has atypical features, some of the classic manifestations of hyperthyroidism are absent. Instead of being excited and nervous, these patients may be subdued and apathetic. There appears to be a disparity between the apathetic facies and hyperactive movements, which may be noted in many of these patients on careful examination. I have found that comparing the movements and the apparent well-being of the patient with the extent of the symptoms is often helpful. Patients who have apathetic facies may have tremor. The patients I have seen appear less often to have tremor with apathetic facies and more often to have hyperactive movements. Levine has commented on the very quick movements of patients with thyrotoxicosis, even if the other manifestations are absent. The so-called "salmon skin" which Levine has emphasized, with hyperemia and increased peripheral blood flow, is often a helpful sign. It was present in the second patient presented today.

3. Cardiac manifestations, mainly atrial fibrillation, may precede the other clinical manifestations of thyrotoxicosis by months or years. On several occasions we have received credit for an

astute diagnosis of thyrotoxicosis in patients with cardiac symptoms present for several months, often after the diagnosis had been excluded earlier in the course of the disease. It is important to emphasize that such patients require careful observation and repeat studies for thyroid disease long after the initial appearance of atrial fibrillation.

The term "masked hyperthyroidism" has been used by Levine to describe a particular condition in persons in whom the hyperthyroidism is not obvious. It was once said that the diagnosis was only masked in the eyes of the physician, not in the patient. The diagnosis of thyrotoxicosis should always be suspected in patients with unexplained atrial fibrillation or congestive heart failure poorly responsive to digitalis therapy or in patients with systolic hypertension with a wide pulse pressure disparity and a normal or short circulation time. This latter finding is in contrast to the delayed circulation time usually seen in patients with cardiac failure.

Evidence of a raised cardiac output including vasodilatation and warm, moist skin is important in differentiating thyrotoxic patients from those with anxiety states, in whom there may be increased sweating but cold and moist skin. Other manifestations of hyperthyroidism, such as unexplained weight loss and diarrhea, may be helpful diagnostic clues. Photomograph measurement of reflex activity may be helpful but in my experience it is less so than in hypothyroidism. Sleeping tachycardia—a finding present in the second patient presented today is important.

The early diagnosis of thyrotoxicosis may influence the subsequent therapeutic results. Sandler and Wilson⁶ emphasized that the response to treatment is not as dramatic in thyrotoxicosis as in myxedema, and may be much less than satisfactory. Twenty percent of the patients they studied died of congestive heart failure within one to seven years after therapy; complete relief of symptoms occurred in only 40 percent. They also demonstrated that survival and the relief of cardiac failure were directly related to the disappearance of atrial fibrillation after treatment. In patients in whom sinus rhythm followed treatment with radio-iodine, no deaths occurred and all patients with cardiac failure were improved. In patients in whom atrial fibrillation persisted, 20 percent died and striking clinical responses were correspondingly less. In studying this report it struck me that one reason for the persistence of atrial fibrillation in so many

patients may have been the authors' fear of using quinidine. Their studies were done before the availability of electrical cardioversion for the treatment of cardiac arrhythmias and they considered congestive heart failure to be a contraindication to quinidine therapy. Hence quinidine was not used to revert the atrial fibrillation to sinus rhythm, and I think that was an error which we would now appreciate. If atrial fibrillation persists after treatment of thyrotoxicosis with radio-iodine, electrical cardioversion should be employed in an attempt to establish normal sinus rhythm.

In summary, the early diagnosis of thyrotoxicosis is important in the prevention of cardiac failure and a poor therapeutic response to radio-iodine.

Heart Disease and Hypothyroidism

Turning to a consideration of the first patient presented today, we encounter a situation in which a good deal of controversy has taken place. A difference of opinion has arisen primarily because there are those who believe that myxedema causes cardiac failure, and there are others who argue that the induction of myxedema has been beneficial in the treatment of congestive failure.

The paradox presented by these differing views may be explained by the fact that myxedema does not cause cardiac failure but does cause pericardial effusion, and pericardial effusion is often confused with cardiac failure. There are many cardiac symptoms and signs in myxedematous patients which suggest the presence of cardiac failure. "Myxedema heart" is a well-known entity described by Zondek in 1918. Fahr³ in Minneapolis was the first to comment that patients with this syndrome have cardiac failure. His conclusions were based almost exclusively on the fact that two-thirds of the patients with myxedema have radiologic enlargement of the cardiac silhouette. More recent physiologic studies have led to the appreciation that cardiac failure is not present and that the enlarged cardiac silhouette is due to pericardial effusion. The cardiac findings in myxedema which have led to the assumption that patients with myxedema have cardiac failure are listed in Table 1. Patients characteristically have exertional fatigue more than dyspnea. They may have angina partly due to associated coronary disease, and they have periorbital and peripheral edema. As radiographically viewed, the heart shadow is enlarged, but the weak and distant heart sound and the difficulty in palpating the apical impulse make an accurate determi-

TABLE 1.—*Cardiac Findings in Myxedema*

1. Exertional fatigue, dyspnea or angina pectoris.
2. Periorbital and peripheral edema.
3. Enlargement of cardiac shadow with:
 - a. weak and distant heart sounds
 - b. difficulty in finding apex beat
 - c. poor cardiac contraction to palpation and fluoroscopy
 - d. small pulse with slow carotid upstroke in face of bradycardia.
4. Relative bradycardia.
5. Effusions in pericardium, pleurae and peritoneum; tamponade rare.
6. Low voltage of QRS, T and P waves on electrocardiogram.
7. Hemodynamic findings:
 - a. decreased O₂ consumption
 - b. decreased cardiac output
 - c. decreased pulse rate
 - d. normal A-V O₂ difference.
 - e. normal response of cardiac output, systemic resistance, and right atrial pressure to exercise.

nation of heart size difficult. The pulse is small, with a slow carotid upstroke, indicating that cardiac contractility is impaired. This latter finding is particularly important because it occurs in the presence of bradycardia when a large stroke output and an increased carotid upstroke would be expected.

The bradycardia may be relative in patients with myxedema. A heart rate of only 60 to 70 would be an unusual finding in a patient with cardiomegaly and presumed congestive heart failure. Although patients may have effusion in the pericardial, pleural and peritoneal cavities, cardiac tamponade is rare. In one patient with myxedema, 4,000 ml of fluid was found in the pericardial cavity, yet the venous pressure was not raised and the patient had no clinical manifestations of tamponade. This indicates the pronounced distensibility of the pericardium if the accumulation of fluid is slow. Low voltage of the QRS complex, as well as the T and P waves, might suggest the presence of cardiac failure in patients with myxedema. Hemodynamic findings, however, demonstrate that patients with "myxedema heart" have decreased pulse rate, normal A-V oxygen difference and a normal response of the cardiac output, peripheral resistance and right atrial pressure to exercise.

Errors in Diagnosis of Myxedema

Errors in the diagnosis of myxedema fall into perhaps four different categories. (1) Because the clinical manifestations of myxedema are often slow and subtle, they are attributed to aging. The patient often seems to be getting older, a little more

tired, a little slower in his thought and movement. (2) Many patients are treated initially for anemia, which tends to be unresponsive to therapy. (3) A diagnosis of nephritis may be suggested by the periorbital edema and generalized serous collections of fluid. Because the edema does not pit, it is thought to be sub-nephritic, and the presence of proteinuria seems to confirm the diagnosis of nephritis. (4) Finally, the diagnosis of cardiomyopathy is often made in myxedematous patients because of the presence of cardiac murmurs and presumed cardiomegaly on radiologic examination.

The long time between the onset of symptoms and the diagnosis of myxedema should be emphasized. Often patients are observed by physicians for five to ten years before the diagnosis is made. In some reports of hypothyroid subjects it may be noted that clear-cut evidence of myxedema and enlargement of the heart shadow had existed for ten years before the diagnosis was made.

The symptoms and signs of myxedema are well known. Apart from the obvious ones there are two that are uncommon and perhaps not fully appreciated. One is the frequency of paresthesias, which in Wayne's⁸ series was 56 percent (in some others as high as 75 percent) and perceptive deafness, which occurred in about half the cases in the series. One interesting finding by Wayne was that the diminution in the lateral one-third of the eyebrows occurred as frequently in the population at large as it did in hypothyroid patients; this sign therefore is of no clinical value. Another symptom frequently helpful in diagnosis is hoarseness. On more than one occasion I have strongly suspected myxedema in a patient with heart disease entirely on the basis of his voice, although the coarse, dry skin changes are often obvious and helpful in diagnosis.

In one large series of cases, myxedema occurred spontaneously in 40 percent of the patients but in the remaining 60 percent it followed either I¹³¹ therapy or thyroidectomy. At the present time many more cases of myxedema are seen following successful I¹³¹ therapy, and it is feared that with the passage of time this proportion will rise progressively. When a patient is given I¹³¹ for thyrotoxicosis and the patient improves, the physician must be alert to the appearance of myxedema in the future.

The evidence that the clinical manifestations of myxedema are due to pericardial effusion rather than to cardiac failure has concerned a number of investigators. Table 2 outlines the evidence sup-

TABLE 2.—*Evidence That Pericardial Effusion Rather Than Cardiac Dilatation Is Responsible For The Enlarged Cardiac Silhouette In Myxedema.*

1. Rarity of clinical congestive failure (rare orthopnea, clear lungs despite apparent cardiac enlargement, no enlargement of liver, no raised venous pressure, no gallop rhythm).
2. Failure of digitalis and diuretics to produce diuresis.
3. Normal response to Valsalva.
4. Normal response of cardiac output, systemic resistance and right atrial pressure to exercise.
5. If pericardial fluid removed and air introduced, cardiac size normal.
6. Patients excrete a large salt load normally.
7. Enlarged cardiac shadow returns completely to normal after thyroid treatment, often within a month. Relapse occurs rapidly, often within a month when thyroid stopped.

porting the contention that the enlarged cardiac silhouette of myxedema is due to pericardial effusion rather than to cardiac dilatation. First is the rarity of clinical congestive failure. Physical signs such as orthopnea, raised venous pressure, enlargement of the liver and gallop rhythm are usually absent in myxedema. Furthermore, as demonstrated by today's first patient, despite an abrupt increase in the heart shadow no evidence of pulmonary venous congestion could be demonstrated. Digitalis and diuretics are usually ineffective. During the Valsalva maneuver, the square wave response of cardiac failure is not present in myxedema. McBrien and Hindle⁵ reported the case of a patient who did show a cardiac failure response to the Valsalva maneuver but did not respond to thyroid therapy and at autopsy was found to have independent heart disease. Following the removal of pericardial fluid, the cardiac size is usually found to be normal. Davies et al² showed that patients with myxedema can excrete normally a large salt load, while patients with congestive heart failure cannot. Last, of course, is the fact that the enlarged heart shadow returns completely to normal after

thyroid therapy, often within a month. Similarly, relapses often occur rapidly when thyroid therapy is stopped.

Table 3 outlines the hemodynamic data of Graettinger et al⁴ in patients with myxedema. The cardiac index is low and increased normally with exercise. There is no important abnormality of systemic resistance. In patients with myxedema systemic resistance fell rapidly with exercise whereas in patients with congestive failure it did not fall with exercise. The right atrial pressure increased with exercise in patients with cardiac failure, but did not change with exercise in patients with myxedema. The cardiac index in myxedema was found to be one-third that in patients with thyrotoxicosis.

In conclusion, the evidence seems quite convincing that pericardial effusion, rather than cardiac failure, is responsible for the large heart shadow in myxedema. The mechanism by which pericardial effusion is produced has never been completely explained. One theory¹ asserts that a mucopolysaccharide complexed with protein exerts osmotic effects within the pericardial sac leading to pericardial effusion. There is also increased capillary permeability because the protein concentration of these fluids is very high.

One remark concerning therapy: The response is very dramatic but may be dangerous. The tendency of many physicians is to administer too much thyroid extract in an attempt to reverse the situation quickly. Severe angina, acute myocardial infarction, cardiac failure, psychosis and ventricular tachycardia may develop within 24 to 72 hours of treatment. It is very important to initiate therapy with a small dose of thyroid extract, perhaps 25 μ g of thyroxine, 5 μ g of tri-iodothyronine or 15 mg of dessicated thyroid. Improvement will occur within days with synthetic compounds, and, unless the patient is threatened with coma, there is no

TABLE 3.—*Comparison of Hemodynamic Data: Hypothyroidism vs. Congestive Failure*

	Hypothyroid n=12		Heart Disease with Failure n=7	
	Rest	Exercise	Rest	Exercise
O ₂ consumption (ml./min./M ²)	87 \pm 3	188 \pm 18	138 \pm 9	202 \pm 17
Cardiac Index (L./min./M ²)	1.88 \pm 0.07	3.05 \pm 0.22	1.93 \pm 0.12	2.11 \pm 0.20
Stroke volume index (ml./beat/M ²)	30 \pm 0.5	39 \pm 0.5	19 \pm 1	17 \pm 1
Heart rate (beats/min.)	64 \pm 3	79 \pm 5	103 \pm 5	122 \pm 4
A-V oxygen difference (ml./100 ml.)	4.66 \pm 0.15	6.15 \pm 0.34	7.18 \pm 0.42	9.83 \pm 0.51
Systemic resistance (dynes cm. sec. ⁻⁵)	2577 \pm 183	1733 \pm 160	2345 \pm 204	2518 \pm 368
Right atrial pressure (mm. Hg)	6 \pm 1	7 \pm 1	10 \pm 3	21 \pm 3

(After Graettinger, 1958)

urgency to reverse the situation abruptly. The harm of too rapid reversal is great.

DR. SMITH: I think we have time for questions or comments.

Question from audience: How extensive is the evidence that cardiac hypertrophy is associated with thyrotoxicosis?

DR. SOKOLOW: There is a good deal of experimental evidence. In animals cardiac hypertrophy can be produced with thyroxine treatment⁷ and in man a complete cure of cardiac failure can follow treatment with antithyrototoxic drugs.

REFERENCES

1. Brewer, D. B.: Myxedema: An autopsy report with histochemical observations on the nature of the mucoid infiltrations, *J. Path. Bact.*, 63:503-512, 1951.
2. Davies, C. E., Mackinnon, J., and Platts, M. M.: Renal circulation and cardiac output in low-output heart failure and in myxedema, *Brit. Med. J.*, 2:595-597, 1952.
3. Fahr, G.: Myxedema heart, *JAMA*, 84:345-349, 1925.
4. Graettinger, J. S., Muenster, J. J., Checchia, C. S., Grissom, R. L., and Campbell, J. A.: A correlation of clinical and hemodynamic studies in patients with hypothyroidism, *J. Clin. Invest.*, 37:502-510, 1958.
5. McBrien, D. J. and Hindle, W.: Myxedema and heart failure, *Lancet*, 1:1066-1068, 1963.
6. Sandler, G., and Wilson, G. M.: The nature and prognosis of heart disease in thyrotoxicosis: A review of 150 patients treated with I^{131} , *Quart. J. Med.*, 28:347-369, 1959.
7. Sandler, G., and Wilson, G. M.: The production of cardiac hypertrophy by thyroxine in the rat, *Quart. J. Exper. Physiol.*, 44:282-289, 1959.
8. Wayne, E. J.: Clinical and metabolic studies in thyroid disease, *Brit. Med. J.* 1:78-90, 1960.

SPINAL HYPOTENSION DURING CESAREAN SECTION

How should you treat spinal hypotension in women undergoing cesarean section?

"My first choice is to push the uterus off to the left. Ninety to ninety-five percent of the mothers will respond to this easily and with no trouble at all. Oxygen always. I am not too sure what this does, but it is good for the mother and good for the anesthesiologist and the obstetrician. A vasopressor I will use in the rare instance when uterine displacement doesn't raise the blood pressure . . . or I will use it when I feel that I cannot keep the uterus off to the left. If I am going to push it off to the left and go do something and then the blood pressure falls right back down again just as soon as the uterus leans on the vena cava again, this is not going to be worthwhile. The babies will do far worse than if you use a vasopressor straightforward or keep the uterus off to the side. So if you can, if you have an extra hand, and you can keep it over there, I would say this is the better technique; if you cannot assure a continuous uterine displacement to the left, then use a vasopressor. What I do is give 25 mg of ephedrine intravenously once, or twice if the first dose doesn't quickly correct the hypotension. I rarely use intravenous fluids other than whole blood, if that be necessary. Postural technique is of interest, but it's often hard to do a cesarean section with the woman's legs up in the air or with the woman on her side."

—FRANK MOYA, M.D., Miami, Florida
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CASE REPORTS

Acute Renal Failure Due to a Bismuth Preparation

JOHN A. JAMES., M.B., *Los Angeles*

IT IS WELL KNOWN that the salts of bismuth are toxic to the kidney. It may be less widely known that oral preparations containing soluble bismuth salts are still available on prescription, and that these may cause serious damage in doses which are not greatly in excess of those recommended by the manufacturer for therapeutic use. The following report describes such an occurrence.

Report of a Case

The patient, a 14-year-old girl, became ill with a cold, sore throat and a dry non-productive cough 17 days before admission to hospital. After five days of illness she was seen by a physician, who diagnosed bronchitis and prescribed oral penicillin. At approximately the same time (12 days before admission to hospital) "7 or 8 pain pills" were given to her by a sympathetic friend for whom they had been prescribed as treatment for sore throat. The patient took all of them over a period of a few hours. They were later identified as bismuth sodium triglycollamate (Bistrimate®), each tablet containing 75 mg of elemental bismuth.

Shortly after taking the pills the patient began

to vomit. Vomiting occurred two or three times daily despite treatment with anti-emetics, and she became very tired and weak. Although her urine output decreased, there was no defined period of anuria. No abdominal pain or skin rash was noted at any time. She was transferred to the Los Angeles County-University of Southern California Medical Center when it was determined that she had blood urea nitrogen (BUN) in excess of 150 mg per 100 ml and serum creatinine of 18 mg per 100 ml.

There was no previous history suggesting underlying renal disease. The patient had experienced seizures during the neonatal period and three episodes of seizures occurred subsequently, the last at four years of age. She was treated with anti-convulsants until she was ten years of age. Apart from some emotional instability, probably related to a difficult home situation, her health was good.

On physical examination the patient was observed to be lethargic but not in acute distress. There was no edema. Body weight on admission was 111 pounds and blood pressure was 125/65 mm of mercury. The mouth was dry, but there was no ulceration or pigmentation. No skin rash was detected other than moderate acne vulgaris. She complained of some numbness of the feet and a questionable loss of sensation to light touch was detected over the soles.

Hemoglobin was 12.1 gm per 100 ml of blood, leukocytes 5800 per cu mm, BUN 177 mg per 100 ml, serum sodium 128 mEq, potassium 4.3 mEq and bicarbonate 15 mEq per liter, sugar 120 mg, creatinine 24 mg and uric acid 15.6 mg per 100 ml, albumin 3.5 gm and globulin 3.7 gm per 100 ml and cholesterol 143 mg per 100 ml. No Beta-hemolytic streptococci grew on culture of material from the throat. The antistreptolysin titer was 100 Todd units. No bismuth was detected in a specimen of serum submitted two days after admission. Urinalysis showed specific gravity 1008, 1+ pro-

From the Pediatric Inpatient Service, Los Angeles County-University of Southern California Medical Center, and the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles.

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Reprint requests to: Los Angeles County General Hospital, 1200 North State Street, Los Angeles 90033.

tein, and a positive reaction for glucose; there were 2 to 5 leukocytes and 1 to 2 erythrocytes per high-power field. No casts were seen. A renal scan using I-131 hippuran showed that both kidneys were of normal size but that there was delayed concentration and excretion of the test material.

Clinical Course

Administration of intravenous fluids without potassium was begun to replace the fluid losses resulting from persistent vomiting. In view of the generally good condition of the patient and the absence of hyperkalemia or severe acidosis, it was decided not to undertake dialysis immediately. She was not treated with demercaprol (BAL) because of the long interval which had elapsed between the ingestion of bismuth and her admission to the hospital. She voided urine only once during the first 16 hours after admission, but during the succeeding three days the urine output rose to 3500 ml daily. The daily output, body weight and BUN determinations are shown in Chart 1. Daily urinalysis continued to show 1+ protein and positive reactions for glucose. The blood sugar remained within normal limits throughout. The patient was discharged on the tenth hospital day in good spirits and eating well.

At follow-up examination three weeks later, she had no complaints and no physical abnormalities were noted. The blood pressure was 104/62 mm of mercury. Body weight was 109 pounds. BUN was 17 mg per 100 ml. One week later, the BUN was 16 mg and serum creatinine 0.9 mg per 100 ml, and the 24-hour creatinine clearance was 160 liters per 1.73 square meters of body surface area. Protein excretion in the urine was less than 0.1 gram in 24 hours. A routine urine specimen was negative for protein and glucose and an intravenous pyelogram showed no abnormality.

Discussion

The medicinal use of bismuth preparations dates from 1785 and until the introduction of penicillin in the 1940s, combined therapy with arsenicals and bismuth was a standard treatment for syphilis. This combination of drugs is still used in the treatment of amebiasis, and bismuth therapy is still advocated in some texts for the treatment of verrucae, condylomata acuminata and some kinds of chronic dermatosis such as lichen planus, scleroderma and discoid lupus. However, controlled studies of the value of bismuth therapy in skin

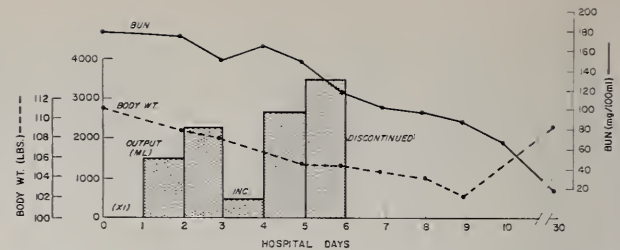


Chart 1.—Urine output, body weight and blood urea nitrogen determinations for patient who had taken "over-dose" of bismuth preparation.

disorders are hard to find. Insoluble bismuth salts such as the sub-carbonate are still used for the symptomatic treatment of diarrhea and in protective creams and pastes.¹ The bismuth is non-toxic in this form, although the subnitrate salt may cause methemoglobinemia.

Soluble bismuth salts have both acute and chronic toxicity, although cases of poisoning have become increasingly uncommon as the indications for bismuth therapy have diminished. The symptoms of acute poisoning include vomiting, skin rashes (the erythema of the 9th day) oliguria or anuria, jaundice and stomatitis.^{1,2,3} Symptoms of more chronic toxicity include a bismuth line on the gums, pigmentation of the soft palate and cheeks and, rarely, of the skin (bismuthia). Peripheral neuritis is a rare manifestation. A bismuth line of increased density may be seen radiographically at the growing ends of the long bones in children.

Ninety percent of absorbed bismuth is excreted through the kidneys, and acute parenchymal renal failure with oliguria is the most severe manifestation of bismuth nephrotoxicity.^{2,3,4,5} In less severe cases there may be a moderate increase in the BUN, proteinuria and a Fanconi syndrome with glycosuria, phosphaturia and aminoaciduria.⁶ Proteinuria and glycosuria were observed in the present case. The nature of the physiologic disturbances that have been reported, as well as the microscopic findings at autopsy, suggest that the principal site of injury is the proximal tubule. Distinctive intranuclear and intracytoplasmic inclusions are commonly found within the proximal tubular cells at autopsy in cases of chronic bismuth intoxication.^{7,8} The nature of the renal injury due to bismuth is unknown but, like mercury, bismuth may inactivate the sulfhydryl groups necessary for active tubular transport processes.

The sequence of events in the present case, namely persistent vomiting and lethargy, followed by the development of acute renal failure, is typi-

cal of acute bismuth toxicity. We have no reason to believe that the patient took more than 525 to 600 mg of bismuth ("7 or 8 pills" of 75 mg each) although no other means of verifying her account of the incident is available to us. The manufacturer of Bistrimate* recommends a dose of one or two tablets three times daily for seven to ten days for treatment of "chronic sore throat." Accordingly, the dose taken by the patient over a period of a few hours was about three times the recommended daily adult dose. There was no evidence, either from the history or from the renal function studies performed after recovery, that the patient had any preexisting renal disease.

Urizar and Vernier⁵ recently were able to collect reports of 30 cases of fatal and non-fatal bismuth nephrotoxicity in children from the literature over the past 25 years. In most cases the bismuth had been given by injection for the treatment of stomatitis or warts. Since there is little evidence that bismuth is of any therapeutic value in these disorders, and since bismuth therapy for other diseases has become obsolete, there seems no good reason why bismuth preparations should continue to be marketed. Certainly physicians and patients may reasonably expect that preparations offered for the symptomatic treatment of sore throat will be free from serious toxicity, even should the recommended dose be substantially exceeded.

Summary

A case of acute renal failure in a 14-year-old girl due to an oral bismuth preparation is reported. The dose ingested by the patient—not on medical advice—was approximately three times the daily dose recommended by the manufacturer for the treatment of "chronic sore throat." It is difficult to find any justification for the continued use of such preparations.

*Smith, Miller and Patch, Inc., New York.

REFERENCES

1. Goodman, L. S., Gilman, A.: *The Pharmacological Basis of Therapeutics*—3rd Edition, The Macmillan Co., New York, 1965.
2. Karelitz, S., Freedman, A. D.: Hepatitis and nephrosis due to soluble bismuth, *Pediatrics*, 8:772, Dec. 1951.
3. Sterne, T. L., Whitaker, C., Webb, C. H.: Fatal cases of bismuth intoxication, *J. Louisiana State Med. Soc.*, 107:332, Aug. 1955.
4. Gryboski, J. D., Goroff, S. P.: Bismuth nephrotoxicity, *N. Eng. J. Med.*, 265:1289, 28 Dec. 1961.
5. Urizar, R., Vernier, R. L.: Bismuth nephropathy, *JAMA*, 198:187, 10 Oct. 1966.
6. Czerwinski, A. W., Ginn, H. E.: Bismuth nephrotoxicity, *Amer. J. Med.*, 37:969, Dec. 1964.
7. Beaver, D. L., Burr, R. E.: Bismuth inclusions in the human kidney, *Arch. Path.*, 76:89, July 1963.
8. Burr, R. E., Gotto, A. M., Beaver, D. L.: Isolation and analysis of renal bismuth inclusions, *Toxic. Appl. Pharmacol.*, 7:588, July 1965.

Carotenemia Associated With Papaya Ingestion

DAVID J. COSTANZA, M.D., *San Rafael*

CAROTENEMIA, a well known entity, was first described by Hess and Myers in 1919.¹ The clinical yellowness of the skin is due to the deposit of beta carotene in the fat-soluble stratum corneum. The condition is noted more in areas having a thick cornium (for example, the soles and palms) than in areas without cornium (mucosa, submucosa and subconjunctivae). Carotenemia occurs in cases of excessive ingestion of certain fruits and vegetables as well as in patients with nephrosis, diabetes and hypothyroidism, and it has been associated with myxedema.²

Fruits and vegetables containing quantities of carotene are carrots, squash, oranges, yellow corn, apple juice, butter, eggs, yellow beans, kale, rutabagas, yellow squash, pumpkins, yellow turnips, sweet potatoes, peaches, apricots, parsnips and papayas. Hughes and Wooten³ reported that farmers have learned to feed carrots and pumpkins to dairy cows in winter months so that the butter made from their milk will be a deeper yellow than that which results from hay feedings.

Other causes of a yellowish-red to orange hue of the skin have been reported. In 1960 lycopenemia associated with excessive ingestion of tomato juice was described by Reich, Schwachman and Craig;⁴ they found a yellowish discoloration of the skin and concentration of lycopene in the serum and liver. In 1966 Hughes and Wooten³ reported two patients with orange-colored skin, owing in one case to ingestion of carrots, yellow squash, rutabagas and tomato juice, and in the other to carrots and tomatoes.

In the case reported herein excessive ingestion of papayas caused clinical carotenemia, which

From the Medical Services, San Francisco General Hospital, and the Department of Medicine, University of California School of Medicine, San Francisco.

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Reprint requests to: 710 C Street, San Rafael 94901.

abated when the patient discontinued eating the fruit.

Report of a Case

A 42-year-old Caucasian woman sought medical attention because of development of a lemon-yellow hue of her skin. On questioning she denied eating carrots, squash, oranges or tomatoes but said that she had been eating one and a half to two papayas a day for the past six months.* The weight of the amount eaten daily was about one and a half pounds.†

The patient was well developed and vital signs were normal. The skin was lemon-yellow, particularly on the palms and soles of the feet and in the folds of the skin. The sclerae were white and normal and the subconjunctivae and mucosae were normal. No other pathologic signs were present.

Leukocytes numbered 7,200 per cu mm with normal differential. Serum bilirubin was 0.4 mg per 100 ml indirect and 0.1 mg direct, and serum glutamic pyruvic transaminase was 20 UV units—all within normal limits. The icteric index at 5.8 units and serum carotene at 449 mcg per 100 ml were elevated. Protein-bound iodine was 6.7 mcg, cholesterol 240 mg and blood sugar 88 mg per 100 ml.

Six weeks after cessation of papaya ingestion the icteric index was less than four units and the serum carotene was 158 mcg per 100 ml.

Discussion

Development of yellow skin associated with excessive ingestion of papayas is an uncommon clinical finding. With the aid of MEDLARS at the Biomedical Library of the University of California at Los Angeles, I have been able to find two other

case reports in the medical literature.^{5,6}

Jacobs in 1892 reported a peculiar lemon-yellow color of the skin associated with eating papayas. His patient had been eating one papaya in the afternoon and one after dinner. "She was a healthy, full-blooded European . . . [in whom] . . . all organs function normally." Jacobs said that a colleague told him that this condition was possible, and an "oldtimer" told him that he had heard of a similar occurrence of yellowness due to papayas. He concluded that it occurred "only in full-blooded Europeans who are blonde and have transparent skin." In 1933 De Langden related yellowness of the skin and the eating of excess amounts of fresh vegetables such as tomatoes, carrots, turnips, and occasionally papayas. He alluded to a case but did not describe it in detail. Both Jacobs and De Langden stressed that their patients had no apparent symptoms except the yellowness. They reported no corroborating laboratory information.

In the case reported herein, there was no feeling of illness, and the yellowness and carotenemia were reversed within six weeks after cessation of papaya ingestion and did not recur.

Summary

A case of carotenemia due to papaya ingestion is reported. The condition was corrected after the patient excluded papayas from her diet. There were no adverse effects noted.

REFERENCES

1. Hess, A. F., and Myers, V. C.: Carotenemia: A new clinical picture, *JAMA*, 73:1743-1745, 1919.
2. Escamilla, R. F.: Carotenemia in myxedema: Explanation of typical slightly icteric tint, *J. Clin. Endocrinol. Metab.*, 2:33-35, Jan. 1942.
3. Hughes, J. D., and Wooten, R. L.: The orange people, *JAMA*, 197:730-731, 29 Aug. 1966.
4. Reich, P., Schwachman, H., and Craig, J. M.: Lycopenemia. A variant of carotenemia, *New. Eng. J. Med.*, 262:263-269, 11 Feb. 1960.
5. De Langen, C. D.: Pseudoicterus of Carotinemie door papaya, *Geneesk. Tijdschr. v. Nederl-Indie*, 73:590-1, 9 May 1893.
6. Jacobs, J. K.: Xanthosis papayae, Eene eigenaardige gele verkleuring der huid tengevolge v an het eten v an papajja, *Geneesk. Tijdschr. J. Nederl Indie, Batav.*, XXXII, 726-30, 1892.

* Her husband was a fruit importer.

† Estimated by the author after having been given several papayas by the patient.

Medicare's Experience with Medicine

MERCIA LETON KAHN, *San Francisco*

IN MEDICARE AS IN many other areas, California tops all other states in a number of important aspects. More Part A (hospital) and Part B (physicians') bills have been processed than in any other state. The expenditures per enrollee in both the hospital program and the medical insurance program have been the highest in the nation. In addition to the largest number of participating hospitals, California also has the largest number of Extended Care Facilities participating and represents 22.5 percent of the nation's total. Obviously, California is playing a major role in this new program and will have a definite influence on the course the program will follow in the future.

While I cannot from personal experience speak for the nation as a whole, I can speak for the seven Western States which are within my jurisdiction and can state that California has had some of the most complex and serious problems. However, had it not been for the many progressive innovations previously instituted by the medical profession in California, implementation of the program would have been many times more difficult.

Such things as the California Medical Association's *Relative Value Studies*, organized utilization review programs in hospitals and medical societies, the program of CMA medical staff surveys of hospitals and many other pioneering efforts have provided important foundations for Medicare, not only in California but nationwide. The strong cooperation from the medical community has contributed immeasurably to the job I and my staff could do during the first difficult years. Names of physicians that come readily to mind in this respect are Carl E. Anderson, Joseph F. Boyle, Jean F. Crum, Roberta Fenlon, Donald C. Harrington, George K. Herzog, Jr., Albert G. Miller, John G.

Morrison, William F. Quinn, Pierre Salmon, Marvin J. Shapiro, Samuel R. Sherman, Malcolm C. Todd, Malcolm S. M. Watts, Harry Weinstein, Dwight L. Wilbur, and Richard S. Wilbur. They and many helpful others have been and continue to be involved not only regionally but on the national scene, and the great assistance they have supplied both in formal and informal meetings and consultation, surely made it possible for us to avoid many serious problems. The massive job in California still has "kinks" to be worked out but with continued cooperation of the physicians and others in the health field and as the program becomes better understood, there is in my judgment no reason why California cannot rank first in quality as well as first in quantity. As it has in other things the medical community in California can set an example to the nation on ways and means to administer this program more efficiently and economically.

As the Medicare Program only recently celebrated its second anniversary, it is timely to review the program up this point—including some of the problems we have had and how we have worked them out—and to consider where we are going.

A few statistics indicate the scope of the program. As of 1 July 1968, 19.7 million persons in the nation aged 65 and over were covered under the basic hospital insurance part of Medicare. Of this number, approximately 18.6 million, or 95 percent of the total, have enrolled in the voluntary medical insurance part. In California about one and three-quarter million are covered under hospital insurance with over one and a half million enrolled in Part B medical insurance.

In its first two years of operation the program nationally paid 8.4 billion dollars (6.3 billion dollars under the Part A hospital insurance program and 2.1 billion dollars under Part B medical insurance). Current statistics on a state or local

The author is Regional Representative, Bureau of Health Insurance, Social Security Administration, San Francisco.

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basis are hard to come by, but a measure of the scope of the program in California is that every working day the California carriers (Occidental and California Blue Shield) receive about 21,000 Part B claims from beneficiaries, physicians and suppliers of other covered medical services.

A fortunate outgrowth of the program has been the impetus for further development of the concept of alternate levels of care. Until now, most insurance programs have considered the payment of hospital benefits the ultimate in coverage. Now Medicare has provided coverage in the outpatient hospital area, the Extended Care Facility (ECF), the Home Health Agency (HHA), and the hospital itself. Thus the program has made it easier for physicians to choose the level of care most appropriate to the older patients' medical needs.

For example, 4.2 million bills were paid during the first two years for outpatient hospital services, and 485,000 home health care plans were set up for older people to receive visits from visiting nurses, physical therapists and other health specialists. Since 1 January 1967, there have been 644,000 admissions of Medicare beneficiaries to ECF's. In California more than 250,000 ECF bills have been processed. Bear in mind that before this program was begun the ECF was a virtually nonexistent commodity in the health market, while today in California 888 Extended Care Facilities are participating in the program.

In commenting on the program's second anniversary, Robert M. Ball, Commissioner of Social Security, noted: "The successful operation of Medicare would not have been possible without the cooperation and hard work of thousands of people, both inside and outside the Federal Government."

What the commissioner referred to was that the Government has not acted alone. Involved in the operation of Medicare, along with the Federal Government, are 123 private insurance organizations—Blue Cross and Blue Shield plans and commercial insurance companies who receive and pay Medicare bills under contract with the Federal Government; 6,900 participating hospitals; 4,700 participating ECF's; 2,100 home health agencies; 2,550 certified independent laboratories; and agencies of the 50 different states.

California's health care delivery system is the largest in the nation. Three carriers, California Blue Shield, Occidental and the Travelers (servicing 52,000 railroad retirement beneficiaries) han-

dle the majority of the Part B claims. In addition about 73,000 beneficiaries are members of six group practice prepayment plans which deal directly with the Social Security Administration. The 595 participating hospitals, 888 Extended Care Facilities and 95 Home Health Agencies work with six Part A fiscal intermediaries—Blue Cross of Oakland, Blue Cross of Los Angeles, Mutual of Omaha, Aetna, Travelers, and Kaiser. In addition, the Social Security Administration services directly the State Mental Hygiene hospitals plus several other providers.

The Use of Familiar Frameworks

The huge cooperative effort previously noted has come within the framework of what the medical health services have been familiar with in the past. In other words, this legislation has maintained the separation of government and health care delivery except in matters of quality standards and in the methods of payment. For years the Public Health Service and the medical profession have cooperated in the furtherance of quality standards in the delivery of medical care. The third party payments system has been present for a good number of years. In these two areas Medicare built on previous conditions and improved upon them.

"Medicare enters its third year on a sound administrative basis," Commissioner Ball said. "With experience and the close cooperation of all involved, problems that arose with the launching of the massive program have been eased, and the entire administrative process is under continuous study to assure that it operates at maximum efficiency." The problems that Commissioner Ball referred to were not unexpected, considering the magnitude of the program, the large number of divergent organizations involved in its administration and the newness of some of its concepts.

What have been some of the problems referred to and what has been done to eliminate them?

One problem has been that carriers have had heavy pile-ups in the medical insurance claims processing operation during a large part of the first two years of the program. One of the major factors contributing to this accumulation was the lack of understanding of the claims procedure on the part of beneficiaries. Although now diminishing, this problem remains despite all the informational efforts which preceded the start of Medicare and which still continue. Even now California Blue

Shield receives more than a thousand claims a day containing incorrect health insurance claim numbers.

Another factor which required consideration was the need to familiarize physicians with the information needed by the carriers to determine and pay reasonable charges for services performed. When the Request for Payment Form—the 1490—was first developed with considerable assistance from individual physicians and the AMA, we thought it was a relatively simple form to complete. We have made improvements in this form in an attempt to ease the claims process.

At the same time, we have been conducting comprehensive review of the performance of carriers and intermediaries with regard to their organization, personnel management, claims processing, utilization review, and professional relations. Our purpose is to find out where improvements might be made and to assist the carrier and intermediary in discharging their obligations to both the beneficiaries and the providers of services. Review teams from the Bureau of Health Insurance make regular on-site surveys of administrative and operational activities of the third parties to help meet problems of this kind.

In its approach to all problems the Social Security Administration has used not only its own personnel but leadership of medical and paramedical organizations for guidance. It has used the Public Health Service to aid particularly in the establishment of quality standards. It has also maintained regular and active liaison with physicians in an attempt to analyze the problems and bring them to agreeable solutions. All of this has been done so that the viewpoint of the physicians, the providers and the beneficiaries themselves may be properly considered.

The Social Security Medicare legislation, and the regulation and administrative guidelines that have followed, have all been directed toward keeping the Medicare patient in the mainstream of medical care. This goal has been paramount even though the principle of non-interference with the patient-physician relationship on occasions has made the program more complex than it might otherwise have been. For example, payment of physicians' services on a "usual and customary" rather than fee-schedule basis has increased administrative complexities. However, this mechanism, which has such universal physician acceptance, has been one of the key provisions designed

to insure high quality medical care for the Medicare patient, and undoubtedly is a cornerstone in the program.

Efforts to Simplify Procedures

The effort to streamline procedures and to cut down paperwork and processing time has been continuous. As problems have been identified, steps have been taken to effect simplification. Some of the time and trouble savers that have been effected are:

- Elimination of date of birth from claim form.
- Dropping physician address.
- Obtaining patient signature only on hospital's own admission forms.
- Grouping outpatient diagnostic procedures instead of listing separately.
- Omitting signature where patient does not visit the hospital. (For example, when specimen is sent to the hospital laboratory.)
- Extension of optional method of billing to hospital-based physicians in addition to radiologists and pathologists.
- Obtaining a blanket assignment from an inpatient for all physician services billed by the hospital during confinement and for all outpatient services billed by the hospital for a stated period up to a year.
- Allowing a physician or clinic to take a blanket assignment for services within the calendar year.
- Eliminating need for California Medi-Cal recipients to sign Medicare billing forms. (This was done by accepting the one-time assignment statement on the reverse of the Medi-Cal identification card.)
- Accepting a physician's stamped signature on Medicare billing forms.

Some problems which became apparent during the program's first year have been the subjects of amendments to the law which were enacted by Congress in late 1967. One problem solved by amendment was the requirement of physician certification of need for admission of Medicare patients to general hospitals and also of the medical necessity for outpatient services. When it became clear that this provision was difficult for many physicians to live with, the Social Security Administration took cognizance of the problem and legislation was introduced in 1967 to eliminate the requirements.

Under another amendment, patients who wish

to pay physicians directly for Medicare services may be provided with the money they need for the purpose on presentation of an itemized bill. Heretofore a receipted bill was required, which meant that the patient had to be out-of-pocket for the time between payment and reimbursement.

While philosophical differences may still exist concerning the program, it is in the main acknowledged that the problems of Medicare are a joint responsibility of government and medicine. Physicians recognize this, just as government representatives recognize that supplying medical care, determining what kind of care is medically necessary and setting acceptable levels of care must remain the physician's responsibility.

Utilization Review

Utilization review also causes problems. The law requires hospitals and ECF's to set up utilization review committees. Utilization review is primarily a function of the medical profession and it requires determinations of not only medical necessity but also whether the most efficient use of available facilities is being made. The effectiveness of utilization review committees has been quite uneven, particularly in the newly established and little understood Extended Care Facility.

Recognizing the problem—for it took the leadership in establishing utilization review as an educational tool as much as 15 years ago—the AMA called a meeting at Houston in the latter part of 1967 to explore pertinent questions. The AMA has also published a handbook for medical societies to use as a guide in helping ECF's secure adequate medical staff and perform the utilization review functions.

The pioneering efforts by the California Medical Association in setting up review mechanisms are well known. Its manual, *Guidelines for Utilization Review*, is used as a guide in many other states. With the medical profession, representatives of the Social Security Administration are currently attempting to solve some of the problems faced in utilization review in various manners: Experimental regional utilization review practice, increasing educational output to the profession, statistical analysis of lengths of patient stays, and communication with the fiscal intermediaries in order to learn the problems in all parts of the country. In California the response of Medicine has been quite impressive with many of the county

medical societies currently providing utilization review for ECF's.

Another difficult problem encountered has been determining the level of care to be supplied to Medicare patients in Extended Care Facilities. In the past, all non-covered care in an extended care facility was identified as "custodial care," which by law is specifically excluded. This was confusing since "custodial care" has different meanings for different professions. Therefore, the term *non-covered* care has been substituted. It now applies to any level of care that is less intensive than *extended care*, which is covered by the law. New guidelines were issued to intermediaries, and they held workshops in August and September with all their extended care facilities. A flyer, "When Care Furnished to ECF Patients Can Be Covered by Medicare," was mailed to physicians. The new guidelines provide for prompter decisions on coverage so that patients and their families will not find themselves in debt for stays they thought would be covered. It is hoped that these actions to bring about a clearer understanding by the patient, the physician and the facility as to just what constitutes non-covered care will reduce the problem of retroactive denial of coverage which has plagued ECF's.

The Social Security Administration has also been taking a very careful look at the Medicare provisions for reimbursing those who provide services. As the readers of this journal no doubt know, institutional providers of services—that is, hospitals, extended care facilities and home health agencies—are reimbursed on the basis of "reasonable cost" of services, while reimbursement for physicians' services and other medical services is based on the "reasonable charge" for such services. In light of the continuing increases in the cost of health care services, the provision in the 1967 amendments for incentive reimbursement experimentation will be directed toward development of incentive to efficiency and economy without adversely affecting the quality of services provided. This presents an opportunity for representatives of health care suppliers to offer study proposals and to volunteer to participate in them. However, such testing can only be carried out with the full cooperation of hospitals, physicians and their organizations.

A discussion of the beginnings of Medicare, its problems and the progress toward solutions leads

logically to the question, "Where does the program go from here?"

We recognize that program evaluation is a continuous process. I hope that I have been able to make it clear that two-way communication and cooperation of the Federal Government, the medical community and the providers of service have been the key to identifying problems and finding ways to solve them. The Social Security Administration welcomes and is responsive to suggestions for improving the program.

No one knows better than the physician what the program has meant to his elderly patients, not only to those who have had serious illness but those who have lived in fear of the financial burden they might have to face. May I close this article with an expression of deep and heartfelt appreciation to the California medical community for the cooperation it has given; and may I quote from three of the many letters we have received from your patients and our beneficiaries for whom the program was designed:

"There are no words full enough to express the gratitude both my mother and

I feel for your sustained help in the pension and the full help of Medicare. You in effect actually gave mother a year of life, not vegetation, and eased the fear of insecurity."

"After a remarkably healthy life, I have fallen victim to cancer of most serious proportions. The outcome is still doubtful, but I am receiving the best treatment now known. My resources are limited, but with the aid of Medicare, I shall be able to have necessary care and to continue the battle without the added worry of finances. I simply must say, 'Thank you'."

"My husband was well on his way to recovery when he had a kidney and bladder infection which took him back to the hospital. We are very grateful for the benefits he has received. It means just the difference between getting along fairly well or going straight plain broke. Accept our thanks."

DISTINGUISHING BETWEEN FORMS OF HEPATITIS

"In the protracted form of viral hepatitis, the onset invariably is acute; and the initial lesions, except possibly for their distribution, are identical with those in acute viral hepatitis. Characteristically, if treatment is begun before the appearance of advanced hepatocellular failure or cirrhosis, the disease is remarkably—although not invariably—responsive to corticosteroid therapy. Even in patients who are untreated, the lesions are not necessarily progressive, and indeed may heal without residuals, or occasionally heal with cirrhosis that remains inactive.

"In contrast, chronic active hepatitis (at least in my experience) invariably has an insidious onset; and usually by the time the disease becomes clinically overt, the lesions already show evidence of chronicity. In my experience I've never seen the early lesion. It is invariably associated with varying degrees of fibrosis and indeed usually with cirrhosis. Characteristically, the disease is progressive and often is relatively resistant to corticosteroid therapy. At best, such therapy may suppress the clinical and biochemical manifestations of the disease, but rarely—if ever—induces a sustained remission without treatment or actual cure."

—GERALD KLATSKIN, M.D., New Haven, Connecticut
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A Conference on the Planning Process

ON JULY 19 AND 20, 1968, the California Medical Education and Research Foundation, with funding from the Bureau of Health Services, Public Health Service, conducted a two-day conference on the Planning Process. The emphasis was on physician and consumer involvement in comprehensive health planning. The more than 150 program participants, reflecting a cross-section of providers, consumers, planners and private and public agencies in California, heard presentations from an expert panel of persons knowledgeable in several fields. Representatives of 12 western state medical associations also participated in the conference. Malcolm C. Todd, M.D., President of the California Medical Association and of its Medical Education and Research Foundation, served as conference chairman. The questions to which the conference addressed itself, and brief summaries of the central ideas which emerged for discussion among the conference participants throughout the meeting, follow.

Goals and Objectives of the Conference

MALCOLM C. TODD, M.D., *President,*
California Medical Education and
Research Foundation

In the eight months since the conference at Chandler, Arizona, Public Law 89-749 was discussed, the medical profession has witnessed a variety of efforts to translate its provisions into a working reality. Through involvement in the formation of state, local, areawide and regional comprehensive health planning councils the physician has been brought closer than ever before to the problems and promises which this law offers. Many individuals and groups are still deeply involved in discussions centering around the nature of cooperative relationships to be developed among all segments of the community, the organizational arrangements to be evolved, and the geographic areas to be defined. But, preoccupation with the organizational aspects and provisions of the Law has tended to obscure the fact that planning, re-

search, goal-setting, decision-making and evaluation represent areas of current priority as they are crucial elements underlying the partnership in which consumers, physicians, official and voluntary agencies, and a wide array of community representation will be concerned.

P.L. 89-749 affords consumers and providers of health care services the opportunity to work together to resolve important problems by means of comprehensive health planning. Historically, this cooperation has taken place on different places along the health care spectrum as special situations arose. This time, it is necessary to look at the problem of health care in its totality, and to arrive at agreement about the priorities which must be established and the creative options and alternatives which must be selected to meet the needs of the community, whether they relate to facilities, manpower, personal health services or to the environment. A challenge is being presented to deal with the future in an imaginative manner by benefiting from the experiences of the past and by correcting the deficiencies of the present. The partnership must be cognizant of the desires and expectations of the public and must seek solutions through innovation and experimentation in order that society may benefit from the knowledge and technology which science offers.

Why Do We Need to Plan?

RICHARD M. BAILEY, Ph.D., *Assistant Professor,*
School of Business Administration,
University of California, Berkeley

Medical services, like other goods and services, have been produced largely in response to "effective demand"—not in response to real medical "need". As a result, income and price constraints have served to ration medical services. Because of these economic factors, patient demand for medical services has been skewed toward the purchase of services for direct relief from discomfort. Thus, physicians' services have been tailored to the individual patients' requirements for repairing damage that has been done. This has usually been ac-

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complished with the addition of personalized attention of the physician which is necessary in such cases.

Physicians have not behaved like most other "producers" attempting to generate new demand—there seems to be little physician interest in selling services which might protect the patient from future illness or accidents. Physicians' services have been curative primarily because they can be easily sold. Such services do not cover the total spectrum of services which should be provided.

Three categories of services are considered as representing the various types of demand for medical care in our society. These are:

1. Services to treat emergency or serious medical problems. These services are stressed most because they are obviously most important in the short-run.

2. Services to treat acute-but-not-life-threatening and chronic conditions. There is an increasing demand for health services for these problems which seem to be a direct function of increasing levels of income.

3. Preventive services. Use of such services increases only slightly with higher income. Relatively few persons see their physicians for regular check-ups, in part because of economic barriers to use (high cost) and in part because of consumer ignorance of the benefits of such services.

For the medical market to operate effectively, it is important that there be a high degree of competition and that the consumer be knowledgeable in his choice of available services. The health industry does not meet these criteria; hence, it is not correct to say that the marketplace alone can resolve the many problems that we have in the production, distribution, and availability of health services today.

Three reasons are offered by economists to explain government's growing involvement in medical care. They are: (1) to provide certain services which are absent from the normal market setting; (2) to effect income redistribution (*e.g.*, social security and welfare medical programs); and (3) to purchase goods and services which the private market does not provide either part or all of the time. There is, in addition, the view that investment in the health of people today may prevent more serious and more expensive problems in the future.

Government has several options or alternatives it can pursue. They are: (1) to enlarge its role as

a producer of health services, or (2) to behave as a collective consumer and therefore *act* as a consumer. While the medical profession has traditionally asserted that medical care is a privilege, public policy has in recent years declared that medical care is a right. This fundamental difference in philosophy has its counterpart in concepts about the future production of health services. Government now is interested in encouraging the production of new services (preventive care) and in promoting new organizational forms for the delivery of health services. These attitudes flow quite naturally from its role as an informed consumer and its interest in purchasing services at a point in time where they can be most effective—not only trying to repair damages after they have been incurred.

The implications of government's role are: (1) more funding of medical services that will result in a greater pay-off to society in the long-run and; (2) reorganization of health care institutions to promote greater efficiency and productivity by use of financial incentives encouraging such action.

What Was the Backdrop for the Philosophy and Concept of Comprehensive Health Planning

HENRIK L. BLUM, M.D., *Clinical Professor of Community Health Planning, School of Public Health, University of California, Berkeley*

While the provision of health services is among the major factors in creating a state of well-being in patients, there are other factors which are at least as important, if not more so, in affecting such well-being. They are: (1) genetics, (2) environment, including physical, educational, economic and social, and (3) personal habits and health behavior. If this assumption is accepted, it is not reasonable to place the entire burden of maintaining health upon the medical profession alone. Physicians and consumers must join ranks to decrease infant mortality, to extend life expectancy, and to improve the quality of living in the United States which does not compare favorably with that of other countries.

A workable definition of planning involves a desire to change, based on dissatisfaction with the present situation, and the necessity of intervention to effect a change. The decision as to when to intervene can be determined by assessment of the situation by looking at both the future and the past. However, it is incorrect to assume that tomorrow is like today, that the past can neatly be

projected into the future based on established cycles, or that plans can be made based on analogous situations.

It is necessary to have imaginative innovators who deviate from the usual means of assessment and projection—people who make things happen. These innovators must look at the population being served and realistically determine if habits as well as needs are being considered; in many cases facilities are available, but are not utilized merely because this factor has been overlooked. Something tangible must be done in specific areas of concern with regard to the consumer population, not only in relationship to health, but to all environmental situations which have an impact on health. This means looking at a community and to its deviances and disabilities and noticing areas of overlapping, considering education, economics, employment, and welfare. It is imperative that an extensive analysis encompassing costs, benefits, and side effects, and alternatives be carefully worked out if a practicable program of comprehensive health planning is to be implemented.

What Are the Components of the Planning Process?

MARK S. BLUMBERG, M.D., *Director of Health Planning, University of California, Berkeley*

While each planning objective has a distinctive feature, all planning shares enough in common to outline certain guidelines and components. The first generalization which may be applied to planning is that it must have a scope of interests. This, in turn, is broken down as follows:

1. Goals must be established based on geographic area and the population concerned.
2. The specific nature of health services, be they mental health, environmental health, personal health, preventive services, or whatever, must be defined.
3. A time frame must be considered as to how long- or short-range the program will be.
4. The amount of authority the group has must be evaluated with regard to how the public will accept suggestions.
5. A basis of existence must be reviewed, considering not only the source of funds, but also the time expended and volunteered.
6. Other planners in the community must be identified and their relationship to a particular program should be recognized.
7. A history of planning in the area should be

developed to avoid repeating prior mistakes.

Secondly, a basic objective should be formulated; this should be fixed to the extent that goals do not shift from planning meeting to planning meeting.

Thirdly, a measure of the objectives, preferably quantitative, should be established.

And, finally, the constraints of the area selected should be reviewed. This includes regulations, laws, and codes to be adhered to.

It is necessary that someone plan the planning; that is, agencies should not just spring up without considering the above guidelines.

The foregoing represent external constraints to planning; the internal constraints relate to how much manpower is available, how much information is secured on the problem, how much money is available, and what the state of the art in planning is in a given area. A model should be developed which, in essence, is a description which relates input to output. This model is tested by obtaining data. Then, planning involves preparing alternative courses of action, reviewing such courses of action, embarking upon a program, and evaluating and coming up with a new plan, if necessary. Planning is a dynamic process and must be followed up in order to revise plans and keep them current.

Expectations of the Federal Agency

R. LESLIE SMITH, M.D., *Assistant Surgeon General, U.S. Public Health Service, San Francisco*

Planning should contribute to the good health of the public to the maximum extent possible. Essentially, planning is a basis for doing. Comprehensive health planning is less concerned with specific goals than it is with trends and directions. The health planning partnership must be strong enough to make a rapid and effective concerted response at all levels. The demands may be general, such as the Poor People's Campaign demands on the Department of Health, Education and Welfare, or may arise from a situation unique to a particular locality, but in either case will require this co-operative response.

There are several broad expectations of the planning process:

1. That health units of a community will be assisted in operational planning and relating their planning efforts to each other.
2. That the broad federal, state, local public and

private partnership can be developed which will respond promptly to the changing aspirations of society.

3. That planning will result in strengthening the leadership and capacities of state health agencies through the utilization of grants.

4. That the state comprehensive health agency will be the official voice in the state, demonstrating the necessity of broad representation of state health interests, particularly of the poor.

5. That the real or imagined hazards related to P.L. 89-749 be recognized.

a. The idea that central government has one master plan for all communities; such a plan does not exist, and indeed, the trend seems to be in an opposite direction;

b. The danger of rigidity in planning and in fixed courses of action;

c. The danger that planning will become an end in itself rather than the means to an end;

d. The problem of planning becoming divorced from those who carry out or are affected by the action.

Planning can be most effective when a climate is created which will permit each individual and organization to select and to participate in objectives which will yield the greatest good for all. Such objectives must be both sensitive and compassionate.

Expectations of the State Agency

JOHN DERRY, *Chief, Comprehensive Health Planning, California State Department of Public Health, Berkeley*

California has pioneered standards and regulations for many health services and related facilities and has an excellent foundation for comprehensive health planning. In the past, state and local officials and agencies have complained about the rigid control and restrictions over the use of Federal funds. However, P.L. 89-749 has made possible greater flexibility and has assured local agencies a part in the decision-making end of the planning process. The emphasis for planning at all levels must be on an on-going process of review, evaluation and implementation to meet changing needs.

The 20-member California State Health Planning Council, seven of which are consumers, consists of a committee working on criteria for the composition of planning organizations and a committee working on definitions of planning. Additional committees enable the Council to work

in conjunction with various voluntary and public agencies in designated health fields.

The State Department of Public Health was given a coordinating function rather than being designated as a central planning agency to collect and resolve all health problems.

The state and local communities have the responsibility to assume the principal task of planning, organizing and administering health services. This implies broad community-wide involvement, particularly the active participation of users and potential users of health care programs.

Coordinated efforts between agencies at state, area, or community levels must be expended to achieve the desired goals and objectives of comprehensive health planning.

Examples of organizational planning efforts are the Health Manpower Council of California, which has responded to concerns over effective utilization of health manpower resources, and the California Health Data Corporation, which is a resource to assist in securing data for comprehensive health planning programs.

How Do You Organize for Planning?

MARTIN A. PALEY, *Executive Director, Bay Area Health Facilities Planning Association, San Francisco*

There is an important distinction between corporate and community planning. The former involves central decision-making and authority, whereas community planning does not possess these attributes. Since the present system is highly pluralistic, to redesign health care to respond to a central authority would be neither feasible nor sensible. The idea behind comprehensive health planning is to be helpful, but not to control.

Effective intergroup discussions must reflect confidence among the groups for one another and a basic trust that the decisions arrived at will be the right ones.

It is absolutely necessary that the goals and principles for which a planning organization exists be delineated early in the planning stages. Public policy in the health field is influenced by two opposite value systems: ignorance and consumer knowledge. The "ignorance" ideology, the professional ideology, assumes that the public cannot diagnose its own needs and is not capable of evaluating the calibre of service it receives. The "consumer" ideology says that the consumer is the best judge of his welfare, but does not imply infinite wisdom.

The structure of planning involves identifying the task or purpose of a planning program prior to the organizational phase of planning, recognizing the various levels of organization, considering at what level the particular task is best handled, and selecting the planning team and getting people involved who will represent the community.

Four important functions of planning are:

1. Collection of relevant data—to discover what services are available.
2. Projection of needs—encouraging new ideas and innovations.
3. Consultation opportunities—particularly to determine what consumers expect of a planning organization.
4. Evaluation and review of plans.

Ideally, the staff of a planning organization should consist of persons of high interest and initiative who will create challenges to be met and will innovate, since the field has so little history and established patterns to fall back on.

What Are the Techniques to Assure Implementation?

LESLIE CARBERT, *Tax Economist,*
Pacific Gas and Electric Company,
San Francisco

Implementation is a stage, not a separate level, of planning. One of the basic weaknesses in the approach the medical profession takes is focusing on the curative rather than the causal aspects of health care. It must look at the environment with the society as its patient rather than the individual. The public must be made aware of the results of no planning, even if fear is used as a technique to create the idea of what will happen to the human condition if a certain course of action is not pursued. The posture of the planning process is more important. This can be accomplished by stating objectives clearly, by conducting adequate research into all areas of the human condition, and by employing the techniques of fear and persuasion as well as financial inducement.

A new governmental form should be created which would permit the making of decisions at the regional level.

Expectations of the Consumer

JOSEPH BELARDI, *President,*
San Francisco Labor Council,
San Francisco

Through vigorous cooperative efforts, the con-

sumer can communicate with the health care field and effect changes to his benefit. However, desired advances can occur only through better organization.

An example of such organization can be seen in an historical review of the situation of the hotel and restaurant unions in the San Francisco area. Many years ago, when an illness could deplete the life savings of a worker, steps were first taken toward the evolution of health plans. By 1950, health plans had become a fringe benefit at the bargaining table. Two major problems at this time were the problem of reimbursement for surgical benefits and the fact that Kaiser plan had been selected for some, but not others. Eventually, a dual choice program was worked out involving both Blue Shield and Kaiser.

The rising costs of medical care have become an issue of concern to many, particularly those in non-covered poverty groups who feel that the efforts of unions cause medical costs to rise beyond their economic reach. The Social Security Director of the AFL-CIO has recently called for hospital efficiency incentives and controls on physicians' fees to curtail this increase in costs.

The Secretary of Health, Education and Welfare has said that pressures for control by government will arise if such fee increases are not curtailed.

It is of greatest importance that such problems not be ignored. The most effective way to handle them is through an organized cooperative effort involving the consumer and all facets of the health care field.

What Are the Techniques of Evaluation?

MARK S. BLUMBERG, M.D.,
Director of Health Planning,
University of California, Berkeley

Government is necessarily involved in health planning because the normal market cannot be trusted to evolve in the ideal direction. This is true for several reasons:

1. The consumer cannot make wise choices for his own benefit;
2. The ethics and professionalism of the health professions keeps the consumer in the dark;
3. Consumers do no "comparison shopping" because of the personal nature of health care services;

4. The health market is slow in responding to needs since advances in research are not foreseeable.

The goals of a planning agency are not easily defined. A seemingly obvious goal is acceptance; however, examination of this objective shows that it is difficult to define the public by whom acceptance is desired. Furthermore, this measure is really only of value over the short run. Size of an agency as a measurement of success is an elusive measure since it says little about the impact made on health.

The best measures of planning are those related to dollar costs and money saved through planning efforts. Such costs are measured in the areas of dollar costs of disability, personal costs (such as discomfort, worry, waiting)—which are difficult to measure but which still represent some dollar value, direct costs of health care, and costs of health supportive activities, such as research. If more is spent on health care services and the quality of care is raised, as indicated by a decrease in the cost of disability, the program is successful.

The American consumer is unsophisticated in the area of health care. He will have to be taught to be a planner and when this is done, he will have become a lay planner and will no longer be the average consumer.

A Case Presentation of Health Planning In Santa Clara County

GERALD BESSON, M.D., *Past President,
Santa Clara County Medical Society,
Sunnyvale*

Three cases of health planning were presented by Dr. Gerald Besson. The first represented planning as a response to a crisis using a narrow base of community participation for the decision-making process. This case considered a marginal income area which was rejected by the Office of Economic Opportunity (OEO) and which demonstrated immediate unmet health needs. The problem was alleviated by forming a coalition of political and professional forces to provide needed services.

The second case was that of planning on a broader community base in response to a health need which was imminent, but not yet at the crisis stage. Specifically, the problem involved the growing inadequacy of allied health manpower both locally and nationally. The goal of the planners was to recruit and train such manpower.

The third case demonstrated planning using the broadest based coordinated community involvement—planning in a systematic rational way. In this case a county-wide regional Comprehensive Health Planning Council was created, based upon the desire to become involved in the potentials of Public Law 89-749.



The Scope and Responsibility of Medicine

A Forum with a Purpose

To engender discussion of what the scope and responsibility of medicine ought to be in today's society, CALIFORNIA MEDICINE printed in its June issue six essays by authors known to have keen if various interest in the subject.

In presenting the essays the editors expressed hope that they would be the beginning of a forum from which a definition of our profession's responsibilities may be distilled. Readers were invited to take part in a continuation of the forum in succeeding issues. Following are two contributions selected from those received to date. Others will be published in the months ahead.

If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102. Keep your essays short, please.

ROGER O. EGEBERG, M.D.

Los Angeles

Dean, School of Medicine, University of Southern California

YOUR SERIES ON THE scope and responsibility of medicine has been eye-opening, stimulating, revealing, and extremely useful to all of us. Anything added at this point must certainly be repetitious, but possibly the following may give emphasis.

The scope of medicine is almost as broad as life; the responsibility is a created charge. The scope of medicine reaches from all of the facets of the healing of the sick to the creation of a health environment for people. It reaches to those matters affecting health such as nutrition, housing, the pressures of life, be they created in rural or urban areas, and even the inputs to our minds. Of all of these as physicians we must be aware, have opinions and, where pertinent, use our talents.

Medicine might be said to have four degrees of responsibility pertaining to this scope. First, medicine has the responsibility for the care of the sick wherever they are or should be. Medicine is responsible for keeping people well through direct intervention, through education, or by its impact in obtaining a healthy environment. Medicine is responsible for returning people to an optimum stage of well-being following illness. Second, in these days of

tumultuous scientific advance, medicine is responsible through institutions and organizations for the maintenance and elevation of the level of professional care, the continuing education and re-education of all physicians. Similarly, medicine is responsible for searching out newer and better ways of delivering health care to the people, not only to the poor but to that self-supporting backbone of America who also wait. Third, medicine must be aware of its close relationship to the allied health professions. It must strengthen them and work cooperatively, warmly, and effectively with them. Medicine is responsible for educating patients and the public, voters, and lawmakers about the needs relating to health.

Congress has voted medical care to 30 or 40 million people who formerly had little or none. We must develop means and methods for caring for these people. Somebody with an eye blind to statistics has suggested that these people be brought into the so-called mainstream of medical care. If this were to be done equitably, and one knows well that it couldn't be, it would average out to 15 hours a week of added work for every man active in the practice of medicine. Since he is now averaging about 65 hours a week, one will have to find a different solution to this problem long before existing or new medical schools can add appreciably to the number of doctors practicing medicine.

Fourth, medicine must look about to those things that affect health, but which are not directly in medicine, and in this area it must have an opinion, collective to a degree and individual. This is the area of education, housing, nutrition, circumstances of work, travel and the many, many factors that make living in a large urban environment increasingly difficult and unhealthy.

If we agree that the scope of medicine covers these four areas, then we can assume our individual responsibilities for that which comes within our purview—we can support those problems which as a profession we should be supporting and exploring, we can urge others better qualified to apply themselves to the problems that affect health but are certainly not problems for our expertise, and finally, we must be aware of problems beyond these and have opinions when they are discussed.

EDWARD B. SHAW, M.D.

San Francisco

*Professor Emeritus, Department of Pediatrics,
University of California, San Francisco, School of Medicine;
Member of the Executive Committee,
Scientific Board of the California Medical Association; and
Member, Scientific Board of the California Medical Association*

LESS THAN FIFTY YEARS AGO, at graduation the medical student was presumed to be equipped for general practice without being limited in his future practice with regard to surgery, obstetrics or the minor specialties. An internship was not obligatory as a preliminary to practice. Many of these graduates entered general practice and attempted almost every type of medical care without any special restrictions—many served acceptably and sometimes with distinction.

Today, at the end of four years the medical student is not equipped for any field of specialized patient care, much less for general practice as it used to be known. The general practitioner is a vanishing breed, especially because of the restriction in access to hospitals for surgical and obstetrical care (except for those with specialty training).

There is now a distinct impetus or at least a pious hope toward developing practitioners who are "family physicians" who will have advanced training in medicine, pediatrics, and general patient care excluding surgery and obstetrics. In effect, these men will cover only the broad field of medicine and pediatrics. (Incidentally, if a classically-derived name could be developed for "the family physician" or "the primary physician," as with orthopedics, pediatrics, ephibiatics, etc., it might improve the image of this form of practice.)

Recently many schools have attempted to indoctrinate students for this type of comprehensive family care by a special emphasis in the medical curriculum. Many great teachers of the past had the capacity to teach the personal attributes of medical care by example, but many of them are now being lost to molecular biology and the super-specialties. Lectures by psychiatrists and sociologists are not the complete substitute for the teaching of empathy and the personalization of medical care as taught by example.

Orientation toward specialty practice has, at the same time, been pushed back to the early years of medical training when the student may set out to be simply a super-specialist and remain completely indifferent to the need to become a "physician." For example: the student

who is determined to become a surgeon may be taught to resort to the psychiatrist if human problems intrude into his technical field, although it is unfair to single out the surgeons. It is worthwhile to point out that, in the past, there have been great physicians in almost every specialty, but this proportion is now dwindling.

Medical schools are not primarily institutes for scientific research or for specialty training below the level of postgraduate education, but unless scientific research and specialty training continue to be strong and essential components of the medical school, they would simply become trade schools with no possibility to contribute to advances in scientific medicine or the development of the specialties—a most dismal and undesirable prospect.

The responsibility of medical schools should be to prepare every student for total patient care within the limits of his personal expertise so that at graduation he would be well-oriented toward all the problems of the patient no matter what special field he finally enters. This concept is as fundamental as the knowledge of gross anatomy to an M.D. The addition of advanced knowledge to the two years devoted to basic science 50 years ago would now require a full four years.

Students could be given this basic education without less emphasis on the basic sciences or neglect of the specialties. They would find time for their special interests; Franklin Delano Roosevelt found time for his stamp collection. Postgraduate education must continue to be an essential part of the medical school, but this should prepare the student for specialty practice, for research, for a career in education, or for family practice. The medical graduate should be a physician with the attributes of human and social consciousness, with empathy and understanding of family and economic situations. His future involvement in research, teaching or family practice should be an extension of his exposure to good teaching, to faculty example and finally, to his own special interests. The student who develops into a surgeon may never do more than hold a retractor in his undergraduate days, but it is the obligation of the school to teach him the fundamental aspects of caring for *people* rather than *patients* before he goes on to specialty training.

An afterthought of what has been said is obviously the product of my own preoccupation with pediatrics. The child is a perfect paradigm of patient care: his problems are often uncomplicated, his history involves his prenatal status, his family background, and his socio-economic situation. He is the patient best suited for initiation of medical students at an early stage of training into all the human aspects of patient care rather than the elderly, complicated, and uncooperative adult patients who form so large a proportion of student case-teaching material.

More emphasis on the child patient for student teaching would be a most useful component for fundamental training in every aspect of practice. Years ago, an elderly golf pro said, "You shouldn't start teaching golf with a driver or much less with a wedge; start out with a putter and slowly work up." Such a principle might readily be acceptable in the training of the medical student. The use of pediatric patients to a greater extent in teaching would necessitate expansion of inpatient and outpatient child care facilities. It must be remembered, however, that if the family physician is to be an increasing factor in the medical care of the population and if his development is to be an important responsibility of the medical school, nearly half of his patients will be children or adolescents. Adequate pediatric training, therefore, should be an important ingredient of routine medical education. Above all, what is learned about the care of the child patient may be the most useful orientation a medical student has for care of patients of all ages.



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EDITORIAL

Bridges Across the Gap

AS THIS ISSUE OF CALIFORNIA MEDICINE goes to press 660 new students are entering California's medical schools, 465 are embarking upon dentistry, 248 are beginning pharmacy and nearly 4,500 are starting out to become nurses. These are young men and women who have chosen to serve their fellow man through one of the health professions. They are fundamentally not very different from the generation which preceded them, unless they are on the average somewhat brighter, better educated when they come to professional school, and perhaps even more deeply committed to the ideal of better health for everyone regardless of his circumstances.

This is not the time or place to discuss their numbers or their qualifications except that both are considerable. Whether California should prepare more nearly the number of health professionals it requires for itself, and perhaps in addition supply some trained personnel for less privileged parts of other nations or the world, are questions of profound moral and practical importance for the years ahead. But today we can simply welcome this impressive group to our midst, confident that their intelligence, education and commitment are such that they will strengthen the quality and bring renewed vigor to the professions they soon will join.

There are many gaps of understanding between

the adult and student generations in present day society. To some degree this has always been true, but in many ways the differences seem sharper than they were. Difficulties often arise because of the attitudes or fancied attitudes which one age group may ascribe to the other, or differences may occur because of sharply changing values. There is much that is new and changing in medicine and there has been lack of communication between generations and some real and fancied attitudes have been ascribed by one generation to the other. A generation gap does exist. It should not be allowed to worsen; rather, it should be lessened.

The editors of CALIFORNIA MEDICINE believe that it is most important that communication between the generations in medicine be strengthened at this time. Person-to-person communication is the best, a people-to-people approach most effective. We believe that this journal can become an important instrument for this purpose if somehow it could reach a substantial number of the 2,000 or so medical students in the state, and reach them on a person-to-person basis. CALIFORNIA MEDICINE strives to reflect not only the latest progress in medical science but also the equally important progress in the efforts of the medical profession to adapt its ancient tradition of service to the social, economic and political realities of the day. In a very real sense, therefore, the journal reflects the common interests shared by both students and practitioners in the betterment of health.

In order to make this journal an instrument of a person-to-person approach of practitioner to student, the editors have established a program for student gift subscription to CALIFORNIA MEDICINE and urge our readers to make use of it. By making one or more gift subscriptions, practicing physi-

cians or even medical societies may establish individual person-to-person bridges with medical students, or with interns or residents for that matter. The recipient may be a medical student or young physician known to the donor or one whose name is picked at random. In either case the name and address of the donor and donee will each be made known to the other.

Such bridges, if there are enough of them, will surely lessen the generation gap.

NOTE: To subscribe, see page 338.

Which New Penicillin?

THE PRESCRIBING PHYSICIAN is confronted by an expanding array of penicillin-like antibiotics from which he attempts to choose an agent by criteria that may be difficult to weigh in relation to one another and which in some respects are frankly ephemeral. Hoeprich's review in this issue of CALIFORNIA MEDICINE on the current status of the penicillins is thus most timely.

Having summarized some of the available criteria for basing such a decision and having suggested the best penicillinase-resistant compounds available for oral and parenteral use, he emphasizes that the sole indication for their use is infection with penicillinase-producing *Staphylococcus aureus*. This restriction, legitimate on grounds both of cost and efficacy, is made more pressing by increasing reports in Europe and the United States¹ of the appearance of clinically significant strains of *S. aureus* resistant to these new antibiotics. Such strains can only be spread more rapidly by the selective effects attendant on promiscuous and unwarranted use of the penicillinase-resistant penicillins. However, penicillinase-producing strains of *S. aureus* are not uncommon in the community, and patients with severe staphylococcal infection should receive a penicillinase-resistant penicillin pending sensitivity test results. The antibiotic should be given by the parenteral route—there is no place for oral therapy in severe sepsis.

The availability of ampicillin has ushered in a new therapeutic era of penicillin usage against infections with Gram-negative organisms. Studies *in vitro* of the activity of ampicillin versus penicillin

G do not show a very striking advantage for the newer compound, and earlier failures of penicillin G likely were the result of inadequate dosage. With parenteral therapy particularly, the advantages of ampicillin can usually be obtained with higher doses of penicillin G at a lower net cost, for ampicillin costs approximately 13 times as much as penicillin G on a weight basis.

Because of its relative usefulness in Gram-negative infection, ampicillin is sometimes ordered for such diseases acquired in the hospital. These are all too frequently caused by ampicillin-resistant strains of *E. coli* and by species which are universally-resistant such as *Klebsiella*, *Enterobacter*, *Pseudomonas aeruginosa*, *Herellea*, and *Serratia*. The danger of prescribing ampicillin in such situations is exemplified in the review by the patient being treated for H. influenza pneumonia. Ampicillin should not be used in hospital-acquired Gram-negative infection unless the sensitivity of the organism is actually known.

Despite its newness, ampicillin is not resistant to the action of staphylococcal penicillinase, and is generally less efficacious against Gram-positive species than penicillin G, with the possible exception of the enterococcus. Although several studies have found ampicillin to be somewhat more active against the enterococcus than penicillin G, the differences are not pronounced. They could readily be compensated for by administering larger amounts of penicillin G. Occasional reports of bactericidal activity of ampicillin alone do exist, but the example given by the reviewer is not striking, a low activity only being realized *in vivo* after the addition of another antibiotic. Such failure is not remarkable in view of the limited information available on reasons for the effectiveness of combined penicillin G-streptomycin or penicillin G-kanamycin regimens when compared with penicillin alone.² In the absence of more than a single published report of cure of enterococcal endocarditis by ampicillin alone³ or of any controlled observations, the basic treatment for this disease must remain a combination of penicillin G and streptomycin, one of the relatively rare instances where combined antibiotic therapy has in fact been shown to be useful.

As far as is known, the new penicillins are cross-reactive in patients allergic to penicillin G. A history, correct or not, of allergic sensitivity to penicillin not infrequently prevents, or at least delays, the administration of optimal antibiotic treatment

to patients. The need for a safe and reliable means of testing for penicillin hypersensitivity, particularly of the immediate, life-threatening type, remains to be definitively met. In its absence, physicians should be most circumspect in making the diagnosis of allergic sensitivity to penicillin. One type of reaction to procaine penicillin G has recently been identified by Tompsett⁴ as a toxicity of inadvertent intravenous administration of procaine rather than allergic response to the antibiotic moiety.

Currently under development are further modifications of the penicillin molecule which will provide activity against pathogens now requiring more toxic drugs. The development of highly specific chemotherapy is the promise of the future—a regimen which will attack the pathogen without altering the normally protective indigenous bacterial flora. Only at that time will we have some hope of breaking the cycle of infection, therapy and superinfection with progressively less treatable organisms, which so frequently characterizes the clinical course of the compromised patient.

REFERENCES

1. Barrett, F. F., McGehee, R. F., Jr., and Finland, M.: Methicillin-resistant *Staphylococcus aureus* at Boston City Hospital, *New Eng. J. Med.*, 279:441-448, 29 Aug. 1968.
2. Hewitt, W. L., Seligman, S. J., and Deigh, R. A.: Kinetics of the Synergism of penicillin-streptomycin and penicillin-kanamycin for enterococci and its relationship to L-phase variants, *J. Lab. Clin. Med.*, 67:792-807, May, 1966.
3. Beatty, H. N., Turck, M., and Petersdorf, R. C.: Ampicillin in the treatment of enterococcal endocarditis, *Ann. Intern. Med.*, 65:701-707, Oct. 1966.
4. Tompsett, R.: Pseudoanaphylactic reactions to procaine penicillin G, *Arch. Int. Med.*, 120:565-567, Nov. 1967.

Medicare Today and Tomorrow

MANY, PROBABLY MOST, California physicians opposed the enactment of P.L. 89-97, since known as the Medicare Law. The California Medical Association played an important part in delineating the reasons for the very real concern of the medical profession with what might happen if the King-Anderson Bill were to be passed. It was passed and the long introduction to this great health drama of the 20th century has been concluded. The chronicle of what is to be the outcome has now begun.

James Z. Appel was president of the American

Medical Association at the moment when the 89th Congress made its far reaching decision. Quite simply, and with both candor and statesmanship, he called upon the medical profession to roll up its sleeves and to do all in its power to make this new law of the land work, and to make it work well in interest of better patient care. His call was heeded from within the profession and it was recognized from without. Physicians at the highest levels of organized medicine, those in the middle ranks and those on the front lines of patient care put their shoulders to the wheel in good faith. And in parallel good faith, the Social Security Administration worked closely with the medical profession to create a program which would accomplish the aims of the Congress with a minimal disruption of established patterns of patient care. Mercia Kahn, Regional Representative of the Bureau of Health Insurance, Social Security Administration, San Francisco, on page 321 of this issue gives her view from the standpoint of government of what has been accomplished thus far. It is a pertinent contribution to an important chapter in the Medicare story, and it gives every evidence of being a far happier chapter than many could have expected.

But the chronicle is by no means ended. The villains have still really to make their appearance, but they can be glimpsed now and then on the sidelines. Most of them wear dollar signs. At the moment one is threatening the financial stability of some non-profit hospitals who accept Medicare patients by failing to reimburse what appears to be the true reasonable full cost to the hospital of caring for these patients. Another seeks a scapegoat for rising costs, would wrongly blame it all on physicians' fees, and would seek an arbitrary ceiling on this important incentive to good medical care. And to be sure there are villains also among the providers who by their behavior invite this kind of destructive control.

It is to be hoped that as the Medicare story unfolds, the villains will be exposed for what they are and that the chapters now being written and to be written will be able to document a triumphant success for the open, frank and statesmanlike approach which both the medical profession and the government have been using to date. If this is done it will augur well for the success of Medicare, not only today but tomorrow as well.

Information Systems and Continuing Education

ALFRED W. CHILDS, M.D., *San Francisco*

THE PURPOSE OF CONTINUING EDUCATION is to aid the physician in maintaining or improving his level of professional competence so he may give high quality care to his patients in the hospital or his office. His individual needs should determine the method and content of his program of education. Diagnosis of his educational needs requires an analysis of his clinical performance.

Systems for evaluation of a physician's work in the hospital through medical staff committee reviews and automated record summaries, such as Professional Activities Study and Medical Audit Program, are well developed in accredited hospitals.¹ However, these are not fully utilized for assisting the physician to maintain or improve his level of competence. Indeed, they have yet to encompass the largest part of the physician's work—that conducted in his office. In the future, with the development of closer organizational ties between office and hospital, as seen in hospital-based practice, and with the growth of information systems that link office with hospital, a more useful spectrum of the physician's work is expected to come under scrutiny of the medical staff review programs, since records of office practice will be integrated with those of the hospital. A medical communication system designed by Bell System to link medical care facilities through a computer illustrates one approach to unifying hospital and office records. The physician's office records kept by the computer could be combined with those of his hospital patients to form a complete file of his

patient care services that would be accessible to medical staff review.

Most hospitals currently carry out only a limited quality evaluation through traditional committee functions such as tissue review, utilization review and medical records review. All of these audit functions could be consolidated into a broader medical audit activity to form a better basis for judgment about quality of care. A medical audit of broader scope would use established methods of retrospective case analysis and evaluation, collection and analysis of epidemiologic data, and observation of current medical care as it is rendered. Through a broadly conceived review activity, the medical staff can gain a sound basis for judgment of individual physicians' practices as well as an overall view of the quality of medical care services in the hospital. Such information may be easily translated into a statement of educational needs.

To do this the community hospital staff must link up the broad medical audit with a system of education. The staff can develop and organize its own teaching potential with the assistance of the education consultant in cooperative programs with education institutions. Then, having capability to provide teaching, and with intimate knowledge of the practice of the individual physician, the medical staff committee is prepared to provide an education prescription for the physician and to judge its effectiveness.

Approaches to developing an education program based on this model—a program that is community-based, individualized and linked to an evaluation of medical practice—is illustrated in part by a cooperative program now being carried on between Pacific Medical Center, San Francisco, and community hospitals for improvement of skills in

The author is a member of the Continuing Education Committee, Pacific Medical Center, San Francisco.

Presented at a meeting of the Lane Medical Society, San Francisco, 20 May 1968.

Reprint requests to: Pacific Medical Center, Clay and Webster Streets, San Francisco 94115.

intensive care practice.² Working with the medical staff in the hospital, the education consultant aids in the identification of needs, organization for education activities, and implementation of appropriate teaching. Complementing and supporting programs such as this, our continuing study of education practices aims to define and refine the basic tools of effective continuing education. Focusing on methods of program design and evaluation, faculty development and organization for individualized teaching, we seek new ways to make teaching relevant and effective.

Teaching methods available in the community hospital include case consultation, supervision of patient care or procedures, presentation and discussion of cases by the practitioner, full-time preceptorship programs and the design and conduct of individual reading programs. None of these are new methods, but we hope to apply them to the new purposes and with new connections to the

essential feedback from medical audit activities. The individual is emphasized in design and evaluation of continuing education. Early experience suggests that the benefits of individual-directed teaching and tutorial approaches far exceed those of lecture or conference teaching for a given investment of resources.

To develop the capability to appraise and improve the quality of care in a community hospital requires not only these techniques of education but full acceptance and participation by all medical staff members. The true physician must be both teacher and student and meet the Hippocratic imperative to "impart precept, oral instruction, and all other learning" to fellow physicians.

REFERENCES

1. Lembke, P. A.: Evolution of the medical audit, JAMA, 199:543-550, 20 Feb. 1967.
2. Pacific Medical Center: Training of physicians in skills of intensive care as applicable in small general hospitals, unpublished description of a pilot program under California Regional Medical Program, Area 1, 1968.

Bridge the Generation Gap

REACH OUT TO YOUNG MEDICINE

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California Medical Association

The Smoking Study

A Report of the Attitudes and Habits of California Physicians with Respect to Cigarette Smoking

■ *With funds provided by the California Department of Public Health, on behalf of the Inter-Agency Council on Smoking and Health, the Bureau of Research and Planning of the California Medical Association conducted a large scale study of the professional and personal attitudes and habits of California physicians with respect to cigarette smoking. The project was initiated in the fall of 1966 with a detailed questionnaire mailed to a random sample of California physicians; the analytic phase was begun in the spring of 1967, all aspects of which are not as yet completed.*

This report contains highlights of the general findings of the study, as well as some detail about differences in attitudes and habits of physicians as they are related to age and medical specialty of respondents.

IN THE FALL OF 1966, a detailed four-page questionnaire was sent to a random (one in six) sample of California physicians by the Bureau of Research and Planning. The purpose was to elicit responses to a wide range of questions with regard to cigarette smoking.

In conjunction with any attempt by the medical community, or any sector of it, to mount a major

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General Office, 693 Sutter St., San Francisco 94102 • 415 776-9400	
PAUL S. PARRY	Southern California Office
1515 N. Vermont Ave., Los Angeles 90027 • 213 663-8071	
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Reprint requests to: Bureau of Research and Planning, CMA, 693 Sutter Street, San Francisco 94102.

anti-smoking campaign, it was deemed essential to have an idea of the attitudes toward such a campaign and toward smoking in general of the individual practicing physician, who is the most important link in any communication between medicine and the general public. Response from individual physicians was good, an indication perhaps of their realization of the vital importance of the project; a total of 67.2 percent of physicians sampled returned questionnaires.

Most Physicians Consider Cigarettes a Serious Hazard

Over nine out of ten responding physicians (91.1 percent) expressed the opinion that cigarette smoking constitutes a serious health hazard. When asked to cite the reason(s) for this conclusion, 83.9 percent checked "professional reports or research," 63.5 percent checked "direct experience with patients," 39.6 percent "personal (health experience of family, friends, yourself)" and 15.2 percent "mass media."

Approaches Used with Patients Who Smoke

Table 1 shows the distribution of physicians' approaches to their patients with reference to smoking. The approaches are listed from most active to most passive. A total of 13.0 percent said

TABLE 1.—*Approach Used by Respondents in Dealing with Patients Who Smoke¹*

<i>Approach Used</i>	<i>Percent of Respondents Using</i>	<i>Cumulative Percent</i>
I make it a point to discuss smoking with all my patients and offer all assistance possible	11.3	11.3
I sometimes bring up the subject of smoking even if there is no immediate health hazard and offer to assist any patient who wants to stop smoking	18.4	29.7
I not only discuss the subject of smoking with patients for whom smoking constitutes an immediate danger to health, but also will offer to assist such patients in their efforts to stop smoking	16.8	46.5
Besides the times a patient brings up the subject, I originate it if I think that smoking is immediately harmful to his health	40.5	87.0
I discuss smoking with a patient only if the patient himself brings up the subject	13.0	100.0

¹Excludes respondents who indicated that they do not come in direct contact with patients.

TABLE 2.—*Methods Used to Help Patients Stop Smoking*

<i>Method</i>	<i>Respondents Who Checked Method</i>	
	<i>Number</i>	<i>Percent¹</i>
Direct order	662	27.6
Impress with hazards	2,026	84.6
Suggestion or persuasion	1,123	46.9
Hypnosis	58	2.4
Educational material	388	16.2
Tranquilizers	411	17.2
Anti-smoking drug	191	8.0
Recommend change in diet	92	3.8
Exert pressure on family	184	7.7
Recommend regular exercise	204	8.5
Suggest other habit	324	13.5

¹Percentage of those physicians who do try to help patients stop smoking.

that they discuss smoking only in response to patients' inquiries, the most passive of the choices of approaches. However, 29.7 percent (those checking Approach No. 4 or No. 5) bring up the subject of smoking even if there is no immediate danger to the patient's health. The largest single group (40.5 percent) indicated that they originate the subject of smoking, but only when they feel that it constitutes an immediate health hazard to the patient.

Methods Physicians Use to Discourage Smoking

Physicians who did try to change their patients' smoking habits were asked to check those methods which they employed in these attempts. Responses to this question are indicated in Table 2. Among physicians who said that they at least occasionally try to change patients' smoking habits, "impressing them with hazards" (84.6 percent) and "suggestion or persuasion" (46.9 percent) were the most popular methods. More aggressive tactics were less popular. Only 7.7 percent checked "exerting pressure on spouse or family"; 2.4 percent used hypnosis. With regard to drug therapy, 17.2 and 8.0 percent, respectively, used tranquilizers or anti-smoking drugs.

Association between Smoking and Medical Conditions

Table 3 indicates how physicians viewed the association between cigarette smoking and various conditions. Most physicians are convinced of the association between smoking and cardiovascular disease (88.0 percent), emphysema, and chronic bronchitis (95.6 percent) and lung cancer (89.8 percent). A majority are undecided about bladder cancer; those who considered themselves

TABLE 3.—*Respondent Opinion Concerning Association between Certain Medical Conditions and Smoking*

Medical Condition	Percent Seeing Association	Percent Seeing No Association	Percent Don't Know
Cardiovascular disease	88.0	2.0	10.0
Emphysema and chronic bronchitis	95.6	0.6	3.8
Lung cancer	89.8	1.3	8.9
Bladder cancer	18.3	19.6	62.1
Peptic ulcer	54.6	9.6	35.8

knowledgeable about this were fairly evenly divided in their opinions. A slight majority associated smoking with peptic ulcer; however, more than a third remain undecided.

Majority Favor Ban on Cigarette Advertising

Table 4 shows the degree of agreement with various formal measures proposed to curb smoking. Over 60 percent of respondents thought cigarette advertising should be banned. Over 50 percent endorsed the following measures: enforcing the age limit for buying cigarettes, prohibiting smoking on all school premises, and requiring that the health hazard on the cigarette package also be present in cigarette advertising. Over 40 percent favored the establishment of anti-smoking clinics, restrictions in vending machine locations and increasing the cigarette tax.

Other Respondent Opinions about Smoking

A number of other significant facts concerning physicians' cigarette smoking attitudes and habits are contained in the complete study. Space limitations in this report prevent their inclusion in tabular form. The following information, then, is excerpted from the larger report and does not relate to any of the tables herein contained.

Four out of five respondents (80.1 percent)

TABLE 4.—*Advocacy by Respondents of Formal Measures which Might be Taken to Discourage Cigarette Smoking*

Formal measure	Percent Advocating
Ban cigarette advertising, as has already been done in some countries	62.2
Prohibit cigarette smoking on all school premises	56.6
Require hazards on label also be placed in advertising	52.3
Enforce age limit for buying cigarettes	50.4
Establish anti-smoking clinics to help those who want to stop smoking	47.9
Restrict location of cigarette vending machines . .	43.4
Increase the tax on cigarettes	42.4
Prohibit smoking in all public places	22.9
Indicate amount of the tar and nicotine content on each pack of cigarettes	16.1
Require a filter on all cigarettes	9.3

answered affirmatively to the question: "Do you consider it your responsibility as a physician to participate in an effort to reshape the attitudes of the general public in regard to the hazards of cigarette smoking?" Of specific courses of action suggested for carrying out this responsibility, "setting an example by not using cigarettes" was rated the most effective by the respondents (32.2 percent ranked it as "very effective," 50.8 percent as "somewhat effective").

Physicians were also asked to check and/or write in what they thought to be the main reasons why the present anti-smoking campaign is not more effective. "People regard long-term effects on health as too remote to worry about" was the reason most frequently checked (69.6 percent).

When asked to rate the various media as to their potential effectiveness in alerting the public to the dangers of smoking, most physicians (54.3 percent) rated television (commercials or programs) as very effective; a sizeable group (36.8 percent) also consider physician/patient contact to be very effective. "Pre-teen-agers" and "teen-agers" were the overwhelming choices as target groups for an organized publicity campaign concerning the dangers of smoking.

Concerning which group(s) respondents think "should assume major responsibility in conducting a campaign against smoking," respondents' first choice was physicians (69.5 percent), followed by teachers (51.5 percent) and "youth organizations" (47.3 percent).

These results taken together indicate that physicians are inclined to see that once an individual has developed the habit of cigarette smoking, rational arguments as to its hazards will have only limited effect, these hazards being too remote compared to massive pressure of constant advertising and personal habituation.

Young people are overwhelmingly chosen as the target for anti-smoking publicity, a "get them before they start" approach. Responsibility for this campaign is seen to rest jointly with the medical community and the schools and/or youth organizations.

Of all respondents, 21.3 percent smoke presently, 38.3 percent smoked but quit, and 39.5 percent have never smoked. Smoking habits of the remaining 0.9 percent could not be determined. An investigation into the effects of the physician's personal smoking habits on the answers he gives to questionnaire items is planned.

TABLE 5.—Respondent Opinion as to Hazardous Nature of Cigarette Smoking by Probable Degree of Exposure to Pathology of Smoking

	Probable degree of exposure	Total Respondents	Opinion about Cigarette Smoking			
			A serious health hazard		Not a serious health hazard or do not know	
			Number	Percent	Number	Percent
Maximum		343	324	94.5	19	5.5
Medium		493	458	92.9	35	7.1
Minimum		1,207	1,089	90.2	118	9.8
Unpredictable		853	768	90.0	85	10.0

TABLE 6.—Basis of Respondent Opinion about Hazardous Nature of Cigarette Smoking by Degree of Exposure to Pathology of Smoking

Basis of Opinion	Percents Indicating Specific Basis, by Degree of Exposure			
	Maximum	Medium	Minimum	Unpredictable
Professional reports	84.6	86.0	86.1	78.9
Personal experience	38.8	30.8	42.5	40.7
Direct experience with patients	63.0	80.1	48.6	75.8
Mass media	12.8	10.6	19.3	12.9

Influence of Physician's Medical Specialty

Physicians were divided into four groups according to medical specialty, based on "probable degree of exposure" to the pathology associated with smoking, in order to determine whether such exposure influences his attitudes and habits with regard to smoking, and if so, in what ways. The maximum exposure group contains anesthesiologists, cardiologists, gastroenterologists, pathologists, specialists in pulmonary disease, radiologists and thoracic surgeons. The medium exposure group is comprised of internists and otolaryngologists. The minimal exposure group includes all other specialties except general practice, general preventive medicine, and public health; these latter three specialties comprise the final group, whose exposure is unpredictable.

Table 5 categorizes physician responses to the question "In your opinion, does cigarette smoking constitute a serious health hazard?" according to specialty group. Although the difference between groups is fairly slight, those with high exposure to smoking pathology appear to have a somewhat increased tendency to answer the question in the affirmative.

As can be seen in Table 6, all specialty groups rely primarily on professional reports or research to make their decisions about the harmfulness of cigarette smoking. However, the medium and the

unpredictable groups rely almost as heavily upon direct experience with their patients (these are the groups which contain physicians who generally treat the "whole man," i.e., internists and general practitioners). Less than half of the physicians said that personal experience (of friends, family, and self) constituted a major basis for their opinions; this basis is most prevalent in the minimum exposure group and least prevalent in the medium group. Those with least exposure rely more heavily on mass media than do other specialty groups.

Information contained in Table 7 indicates that all groups are about equally likely to associate cigarette smoking with cardiovascular disease, emphysema and chronic bronchitis, lung cancer and bladder cancer. Over 20 percentage points, however, separate two of the groups with regard to peptic ulcer; while 67.1 percent of general practitioners and others associate it with smoking, only 45.9 percent of the group with minimum exposure do so. About half of all physicians in the first two groups see such an association. A relatively high proportion of respondents indicated that they did not know about relationships between bladder cancer or peptic ulcer and smoking.

Table 8 was prepared in order to determine whether there is any association between current smoking habits of physicians and their degree of exposure to the pathology of smoking. Physicians

TABLE 7.—Percent of Respondents Who Associate Certain Medical Conditions with Smoking by Degree of Exposure to Pathology of Smoking

Medical Condition	Percent Seeing Association by Degree of Exposure			
	Maximum	Medium	Minimum	Unpredictable
Cardio-vascular diseases	89.5	88.6	86.3	89.7
Emphysema and chronic bronchitis	95.9	97.8	94.0	96.7
Lung cancer	90.4	91.9	89.8	88.4
Bladder cancer	21.6	18.5	15.7	20.8
Peptic ulcer	52.5	56.0	45.9	67.1
Other*	11.7	12.4	10.6	13.0

*Includes all others written by respondents.

TABLE 8.—Respondent Cigarette Smoking Habits and Percent of Former Smokers Who Quit by Degree of Exposure to Pathology of Smoking (Percents of Respondents)

Degree of Exposure	Total Respondents*	Smoke Now	Smoking Habits		Percent of Former Smokers Who Quit
			Smoked Formerly	Never Smoked	
Maximum	343	20.1%	36.7%	43.2%	64.6
Medium	490	18.0	45.3	36.7	71.6
Minimum	1,194	22.3	37.6	40.1	62.8
Unpredictable	843	23.0	37.6	39.4	62.0

*Excludes respondents whose smoking habits could not be determined.

with medium exposure—internists and otolaryngologists—are least likely and general practitioners are most likely to smoke currently. It is interesting to note, furthermore, that the group which is least likely to smoke now is also most likely to have smoked previously; 71.6 percent of internists and otolaryngologists who ever smoked have quit.

Figures contained in this table suggest that the impetus for giving up cigarettes comes from stimuli other than a physician's association with the pathology of smoking.

Influence of Physician's Age

Physician respondents were grouped according to age to see what influence this factor has on attitudes and habits with respect to smoking. As was the case with medical specialty, in some aspects a degree of association is demonstrable.

Table 9 presents physician opinion as to the hazardous nature of cigarette smoking. Although, by and large, those physicians 39 years of age and younger are slightly more apt to see smoking as a serious hazard than do their older colleagues, there is, overall, a rather unusual association between age and opinion as to smoking hazard. The percent who reject the idea that it is a serious hazard rises through age 59, drops through age 69, and rises again among the oldest group.

Although not shown in the table, there is a definite association between age and dependence upon "professional reports or research" in making this decision. The older the physician, the less apt

he is to state this as a basis for his decision; the range is from 98.7 percent for the under 35 group to 59.7 percent for the 70 and older group.

Table 10 concerns opinion about the association of specific medical conditions with cigarette smoking. Although the group 34 years of age and younger is more likely than the group 70 and older to associate cigarette smoking with cardiovascular disease (91.3 vs. 82.1 percent), the entire curve is too erratic to discern any age-dependent relationship with regard to this variable. Similarly, although the youngest group is slightly more likely than the oldest group to associate cigarette smoking with emphysema and chronic bronchitis, no meaningful statement as to a "trend" can be made. There is, however, a definite trend with regard to lung cancer; the younger the physician, the more likely he is to associate it with cigarette smoking. The group 34 and younger is also the most apt to associate cigarette smoking with bladder cancer and to specify other diseases or conditions which he considers applicable.

One clear-cut trend with regard to the use of particular methods to help patients stop smoking is that the use of tranquilizers declines with the physicians' increasing age, although, even in the youngest groups, slightly less than one-fourth indicate use of the drugs. Also noteworthy, is the relatively high usage by physicians 70 and older of the "pressure on family" approach; even in this group, however, the proportion is under 20 percent. The degree of feeling of responsibility to

TABLE 9.—Respondent Opinion as to Hazardous Nature of Cigarette Smoking by Age Group of Respondent

Age Group	Total Respondents	Opinion about Smoking			
		Consider It a Serious Health Hazard		Do not Consider It a Serious Health Hazard or Do Not Know	
		Number	Percent	Number	Percent
Under 35	149	145	97.3	4	2.7
35-39	480	459	95.6	21	4.4
40-44	555	515	92.8	40	7.2
45-49	509	463	91.0	46	9.0
50-54	426	378	88.7	48	11.3
55-59	345	292	84.6	53	15.4
60-64	210	190	90.5	20	9.5
65-69	140	129	92.1	11	7.9
70 and older	134	116	86.6	18	13.4

TABLE 10.—Respondent Opinion Concerning Association between Certain Medical Conditions and Smoking by Age Group of Respondents

Age Group	Total Respondents	Percent Seeing Association, by Specific Condition					
		Cardio-Vascular Disease	Emphysema & Chronic Bronchitis	Lung Cancer	Bladder Cancer	Ulcer	Other*
Under 35	149	91.3	98.0	97.3	22.8	56.4	14.8
35-39	480	89.8	98.3	94.2	16.5	50.8	10.8
40-44	555	91.4	96.0	91.9	19.5	55.0	12.8
45-49	509	88.0	96.1	91.6	19.8	57.8	13.0
50-54	426	88.7	94.1	88.7	18.5	53.3	12.0
55-59	345	82.3	94.8	86.4	16.5	54.5	10.7
60-64	210	88.6	94.3	84.8	18.1	59.5	8.6
65-69	140	81.4	91.4	82.1	17.9	45.0	9.3
70 and older	134	82.1	93.3	78.4	13.4	59.0	9.7

*Includes all others written in by respondents.

TABLE 11.—Cigarette Smoking Habits of Respondents and Percent of Former Smokers who Quit by Age Group (Percents of Respondents)

Age Group	Total Respondents*	Smoke Now	Smoking Habits		Percent of Former Smokers Who Quit
			Smoked Formerly	Never Smoked	
Under 35	149	14.1%	30.2%	55.7%	68.2%
35-39	475	22.5	33.7	43.8	59.9
40-44	548	22.1	40.0	37.9	64.4
45-49	506	22.3	35.0	42.7	61.0
50-54	424	23.1	41.3	35.6	64.1
55-59	344	24.4	40.7	34.9	62.5
60-64	209	21.5	45.0	33.5	67.6
65-69	137	16.8	45.2	38.0	72.9
70 and older	129	13.2	43.4	43.3	76.7

*Excludes respondents whose smoking habits could not be determined.

"participate in an effort to reshape the attitudes of the general public in regard to the hazards of cigarette smoking" remains fairly constant at about 85 percent until age 45, after which it dips slightly. There is another dip at age 55. Although a majority of physicians 70 and over still answer this question in the affirmative, the percentage (73.1) is noticeably less than that in the under 35 group (85.2 percent).

Physicians under age 35 are less likely to be smokers than are physicians in the middle ranges of age, as can be seen in Table 11. Smoking decreases at age 65, but this may indicate merely

that some physicians in that age group who did continue to smoke either died or quit practicing medicine. The 34 and younger group is also much more apt to have never smoked than any other age group; the difference between this and the next two age groups is substantial. Of physicians who at one time smoked, those 65 and older are the most apt to have quit.

Copies of the complete study, in which the interested reader will find additional detail both as to the findings and the methodology employed in conducting the study, are available in limited quantities from the Bureau of Research and Planning.

Cervical Cancer Detection and the Registered Nurse

A Joint Statement by the California Medical Association, the California Hospital Association, the California Nurses' Association and the California Conference of Local Health Officers.

TO PROMOTE GOOD patient care, and protect the doctor, the registered nurse, and the institution or agency, the California Nurses' Association, the California Hospital Association, the California Medical Association and the California Conference of Local Health Officers recognize the legal right of registered nurses to take cytological cervical smears for cancer as one of the methods of determining if cancer is present, but only if all the following conditions exist:

1. The technique is to be performed in an agency or institution, and

2. Where the technique is to be performed in an agency or institution, the procedure is to be performed upon the order of a physician. The technique is to be performed within the framework of preparation and procedures for practice of the registered nurse, which have been established for the agency or institution by a committee composed of representatives of the agency or institution, physicians, registered nurses, and administration. This framework of preparation, and of practice is to be reproduced in writing and made available to the total medical and nursing personnel, and

3. It is the jurisdiction of that committee in that agency or institution to:

- a) decide if the registered nurse may perform the technique
- b) determine the preparation to be required of the registered nurse
- c) establish inservice teaching to be required, and
- d) establish the technique or techniques to be used.

June 15, 1968.

Cancer Quackery Curbs

EIGHT CANCER REMEDIES and diagnostic tests are now on the list of quack drugs according to announcement from the Cancer Advisory Council to the California State Department of Health. They are Krebiozen, Hoxsey, Koch Antitoxin, Lincoln Staphage Lysate, Laetrile, Mucorhizin, and the Anthrone tests.

During 1967, criminal or administrative action was brought against seven persons under a state law designed to curb medical quackery in California in cancer diagnosis and treatment. Four were found guilty; two were given warnings after citation hearings; and two were served with cease-and-desist orders, in one case in addition to a court sentence.

California's cancer quackery law, first passed in 1959, was reenacted in 1965 and 1967, when it was significantly strengthened by placing the burden of proof of safety and efficacy of a drug, medicine, compound, or device on the proponent of the agent rather

than requiring the State Department of Health to disprove its usefulness.

In this and other respects, the cancer law is patterned after federal regulations dealing with the use or sale and shipment of new drugs. It also makes violations of regulations or cease-and-desist orders enacted under the law misdemeanors.

Current officers and board members of the Advisory Council are: David A. Wood, M.D., chairman, San Francisco; Helen G. Brown, vice-chairman, Van Nuys; Sol R. Baker, M.D., Los Angeles; Marvel L. Brenner, San Bernardino; John W. Cline, M.D., San Francisco; John E. Connolly, M.D., Los Angeles; Emanuel Fineman, Los Angeles; Thomas S. Nelsen, M.D., Palo Alto; Joseph F. Ross, M.D., Los Angeles; George S. Sharp, M.D., Pasadena; Sol Silverman, Jr., D.D.S.; Ralph J. Thompson, Jr., Loma Linda; Edward Zalta, M.D., Glendora; and Louis M. Saylor, M.D., ex-officio member.

In Memoriam

ADAMS, GEORGE DAVID, La Mesa. Died 24 August 1968, aged 51. Graduate of George Washington University School of Medicine, Washington, D.C., 1943. Licensed in California in 1947. Doctor Adams was a member of the San Diego County Medical Society.



BAUM, MAX, San Francisco. Died 4 September 1968 in San Francisco, aged 74. Graduate of Georg August-Universität Medizinische Fakultät, Göttingen, Prussia, Germany, 1921. Licensed in California in 1942. Doctor Baum was a member of the San Francisco Medical Society.



BEACH, EDWARD WOODBRIDGE, Sacramento. Died 26 August 1968 in Sacramento of subarachnoid hemorrhage, aged 73. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1919. Licensed in California in 1920. Doctor Beach was a member of the Sacramento County Medical Society.



CASTELLO, HENRY MINTOURE, Santa Clara. Died 31 August 1968 in San Jose, aged 42. Graduate of University of Illinois College of Medicine, Chicago, 1950. Licensed in California in 1951. Doctor Castello was a member of the Santa Clara County Medical Society.



CURTIS, LORIS EUGENE, San Francisco. Died 31 August 1968 in San Francisco, aged 64. Graduate of State University of Iowa College of Medicine, Iowa City, 1928. Licensed in California in 1928. Doctor Curtis was a member of the San Francisco Medical Society.



DIEDERICH, OTTO PETER, Fresno. Died 5 August 1968 in Fresno, aged 72. Graduate of Rush Medical College, Chicago, Illinois, 1921. Licensed in California in 1921. Doctor Diederich was a member of the Fresno County Medical Society.



ELLIOTT, HOWARD MANNING, Los Angeles. Died 19 August 1968 in Los Angeles, aged 69. Graduate of the University of Illinois College of Medicine, Chicago, 1927. Licensed in California in 1927. Doctor Elliott was a member of the Los Angeles County Medical Association.



GOREN, MORRIS L., Beverly Hills. Died 15 August 1968 in Los Angeles, aged 60. Graduate of Northwestern University Medical School, Chicago, Illinois, 1936. Licensed in California in 1945. Doctor Goren was a member of the Los Angeles County Medical Association.



IVERSON, PRESTON CHARLES, Panorama City. Died 16 August 1968 in Panorama City, aged 58. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1935. Licensed in California in 1938. Doctor Iverson was a member of the Los Angeles County Medical Association.

KATZ, MILTON, Westminster. Died 17 August 1968 near Monterey in a private plane crash, aged 44. Graduate of Western Reserve University School of Medicine, Cleveland, Ohio, 1956. Licensed in California in 1957. Doctor Katz was a member of the Orange County Medical Association.



LEVIN, HARRY A., Beverly Hills. Died 28 August 1968 in Los Angeles of uremia, aged 72. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1917. Licensed in California in 1917. Doctor Levin was a member of the Los Angeles County Medical Association.



PARKER, JOSEPH A., Los Angeles. Died 16 August 1968 in Los Angeles, aged 75. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1922. Licensed in California in 1922. Doctor Parker was a member of the Los Angeles County Medical Association.



POWERS, KENNETH VERNON, Fullerton. Died 6 August 1968 in Fullerton of carcinomatosis of the thyroid, aged 64. Graduate of Northwestern University Medical School, Chicago, Illinois, 1930. Licensed in California in 1945. Doctor Powers was a retired member of the Orange County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



RAPHAEL, JAMES CLARENCE, Oakland. Died 2 August 1968 in Oakland of acute coronary thrombosis, aged 72. Graduate of University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Doctor Raphael was a member of the Alameda-Contra Costa Medical Association.



SACHS, HERMAN KARL, Irvine. Died 1 August 1968 in Los Angeles of cancer, aged 69. Graduate of Wayne University College of Medicine, Detroit, Michigan, 1921. Licensed in California in 1946. Doctor Sachs was an associate member of the Orange County Medical Association.



SMITH, LEO DUANE, Stockton. Died 22 May 1968 in Stockton of myocardial infarction with complications, aged 67. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Smith was a member of the San Joaquin County Medical Society.



SMITH, ROBERT LEE, Newport Beach. Died 12 August 1968 while scuba diving at Catalina Island, aged 39. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1957. Licensed in California in 1958. Doctor Smith was a member of the Orange County Medical Association.

1969 ANNUAL SCIENTIFIC ASSEMBLY

OF THE CALIFORNIA MEDICAL ASSOCIATION

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LETTERS *to the Editor*

What Goes On?

To the Editor: Even though the advertisements pay for it, this publication [*What Goes On*] in my opinion is another waste of members' money, an unnecessary duplication of printing. This could and should be in CALIFORNIA MEDICINE.

JAMES O'DONOGHUE, M.D.
Redwood City

Treatment of Acute Leukemia

To the Editor: Dr. Cline's discussion of acute leukemia in your August issue was excellent. [Acute Leukemia—Current Concepts of Pathogenesis and Treatment, Medical Staff Conference, CALIFORNIA MEDICINE, 109:146-155, Aug. 1968.] However,

I would like to point out two minor errors on page 151.

Table 2 (Supportive Therapy for patients with Leukemia) includes "Uricosuric agents or xanthine oxidase inhibitors." Since the primary danger of hyperuricemia is renal tubular blockade with urates, uricosuric agents might be harmful rather than beneficial. Decrease in formation of urate by means of allopurinol is certainly the preferred therapy.

Under the heading "Specific Therapy" the name of the drug is misspelled "cytosine arabinocide." The term denotes a compound containing arabinose rather than one lethal to Arabs, so the spelling should be "arabinoside."

DAVID C. STOLINSKY, M.D.
Los Angeles

Dr. Stolinsky is absolutely right, and we are grateful for his keen eyesight. Rather than "uricosuric agents," we meant to indicate that patients in danger of uric acid nephropathy should be placed on a regimen of high fluid intake and may be considered for alkylinization with sodium bicarbonate.

MARTIN J. CLINE, M.D.
San Francisco

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.

Director, State Department of Public Health

Malnutrition in California

IS MALNUTRITION POSSIBLE in the Nation's No. 1 agricultural state, in these years of abundance? The answer is yes. One may eat but not enough; one may eat enough but lack variety; one may be overweight but undernourished. Where is the evidence? It is largely missing. General data can substantiate the above, but specific information on the extent of malnutrition today in the various states is not yet available.

Should we be concerned? Recent findings on food consumption and hunger in the United States have implicated California. In the report "Hunger USA," released this spring by the Citizens' Board of Inquiry into Hunger and Malnutrition in the United States, eight counties in the San Joaquin Valley were classified as having "serious hunger problems." This study was generated by widely publicized eyewitness accounts of starvation in Mississippi by a Senate subcommittee, and by a group of physicians sponsored by the Field Foundation.

The question of whether conditions found in Mississippi prevailed nationally prompted the Citizens' Crusade Against Poverty to establish an independent board of inquiry to obtain such information. The evidence presented in the report was obtained from hearings held in five states, from information supplied by government and private agencies, food industries and physicians.

At the same time, the U.S. Department of Agriculture released findings of its 1965 survey of the food consumption in a nationwide sampling

of 7,500 households. The data indicated that fewer households had good diets in 1965 than in 1955. In California, 16 percent of the state's households had poor diets. This represented 860,000 households or approximately 3,000,000 people.

A third report, "Their Daily Bread," dealing with poverty and hunger in the United States, was published during the year. It stresses the failure of the National School Lunch Program to meet the objective of the original legislation—"to safeguard the health and well-being of the nation's children." The program was intended "to supply lunches without cost or at a reduced cost to all children who are determined by local authorities to be unable to pay the full price thereof" without discrimination. Yet the report shows that only 39,647 school children in California of a total of 396,632 in need benefited. The Church Women United, National Board of YWCA, and the National Councils of Catholic, Jewish, and Negro Women sponsored the investigation.

What do these findings mean in terms of health for Californians? An adequate determination of the effect of poor diets and hunger on state of health requires that the nutritional status of individuals be assessed. This calls for a physical examination, biochemical determinations and a dietary evaluation. Since no study of this magnitude was undertaken, precise information on the extent to which malnutrition is undermining the people's health is not known.

Congressional hearings on the implications of the reports started some action. The Secretary of Health, Education and Welfare was directed to determine the "state of nutrition" in poor areas of nine states: Texas, Louisiana, Michigan, Kentucky, New York, West Virginia, Massachusetts, Washington and California. Only areas in the lower one-fourth income levels of the nation are eligible for such investigation.

Studies are now under way in five states and will start soon in the remaining four. They are directed by Arnold E. Schaefer, Ph.D., Chief of the Nutrition Program, Public Health Service. The work here will survey 5,000 California families (about 20,000 persons) for clinical evaluation of their physical state and food practices. The University of California and other universities in the state will collaborate in the study, with the expectation that more information than the federal study requires will also be gathered and put to use. At this date, we are hopeful that sufficient funds will

be available to start the survey in California by early 1969.

Public concern in California continues to grow over the probability that malnutrition actually is occurring in part of the population in our fertile state. Health and medical professionals, both in the public and private sectors, share with other concerned Californians the responsibility to see that malnutrition in California is brought to an irreducible minimum. The federal survey should provide the information needed to improve the diet of our three million residents suspected of being ill fed.

CLASSIFICATION OF BREAST CANCER

"In the pathological classification [of breast cancer] . . . , we found it very practical to label the different levels in the axilla. A fair number of institutions are doing this now: using a metal tag to delineate the lower third, middle third, and upper third of the axilla. We usually put one tag at the tendon of the pectoral major muscle. That's level one. Level two is behind the pectoralis minor muscle, and level three is the apex. This enables the pathologist to separate the axillary contents into the various levels; and when he reviews the contents and reports the specimen, you have a better idea regarding prognosis, need for x-ray therapy, and so forth. If you have one node involved at level one, it's not nearly as bad a situation as if there's a node involved at level three at the periphery of your operation. We found this method to be very helpful; and in a survey of a large number of patients tagged in this way, the salvage rates with radical mastectomy were roughly 80, 60, 40, and 20 percent when, respectively, all nodes were negative, only level one was involved, only level two, and only level three. As the disease extends from the breast through the lymphatics and goes more peripherally, the prognosis falls because there's a higher chance of a systemic disease being present."

—JEROME A. URBAN, M.D., New York City
Audio-Digest Surgery, Vol. 15, No. 17



Carcinoma In Situ of the Uterine Cervix

A Review of Some Present Clinical Problems

WARREN E. JONES, M.D., *Sacramento*

■ *The vaginal smear reveals a spectrum of borderline lesions of the uterine cervix. This spectrum is the source of new clinical problems involving both the recognition and treatment of these various entities. A review of the literature of the past decade indicates that vaginal smears should be obtained regularly every year or two in all women beginning at the onset of sexual activity, but the initial smear may be falsely negative in 10 to 30 percent of cases. When patients have abnormal smears, the precise diagnosis can be established more accurately by cold-knife conization than by multiple punch biopsy.*

While hysterectomy has been considered "definitive treatment," late recurrence in the vagina occurs in 1.24 percent of patients so treated. A compilation of 1,100 patients with carcinoma in situ of the cervix treated by conization and follow-up smear reveals that in over 90 percent the disease was controlled by the cone alone, and the remainder by repeat cone or hysterectomy.

Precise definition is required in treatment decisions concerning micro-invasive lesions, but these may be well treated by non-radical measures. In almost 500 patients so treated, no death occurred from therapy or tumor metastasis.

When carcinoma in situ is found during pregnancy, a coexisting invasive carcinoma must be excluded by appropriate conization or punch biopsy and definitive therapy completed after vaginal delivery.

DESPITE AN AVALANCHE of published reports on carcinoma in situ of the uterine cervix, the clini-

cian is still faced with annoying problems in the management of this disease. However, a review of some of these writings of the past decade reveals an increased understanding of the lesion and better agreement as to methods of diagnosis and treatment.

From the Sutter Community Hospitals and Mercy General Hospital, Sacramento.

Chairman's Address: Read in part before the Section on Obstetrics and Gynecology at the 97th Annual Session of the California Medical Association, San Francisco, March 23 to 27, 1968.

Reprint requests to: 5301 F Street, Sacramento 95819.

The importance of early treatment for cancer of the uterine cervix has been stressed to generations of physicians, with emphasis on close attention to minor symptoms, periodic examination, frequent biopsy and adequate therapy⁷²; but it was not until publication of the monograph by Papanicolaou and Traut in 1943⁷⁹ that a simple clinical method of detection was available. It was still some years before exfoliative cytology became accepted; and, as late as 1949, Novak⁷⁷ felt that there were "still too many pitfalls and limitations to recommend the general adoption of cytology among practicing gynecologists." The full influence of the monograph was not felt until at least ten years after its publication, when exfoliative cytology was generally accepted.¹⁰⁶

In the past 15 years, the widespread use of "the smear" by generalists and various specialists alike has been associated with dramatic changes in the clinical recognition of carcinoma of the cervix. There has been a clear shift to an earlier stage of disease at the time of first diagnosis, associated with a significant decline in the mortality rate for cervical cancer as reported in California,⁵⁹ Tennessee⁸⁹ and New York.³⁹ Questions have been raised as to whether cytology is solely responsible for this improvement^{4,33}; but the fact remains that in our daily practice we are finding and treating preclinical cervical cancer much more often than ten or fifteen years ago. This is shown by the experience in California where *in situ* cervical cancer as a proportion of all cervical cancer cases increased from zero in 1942, through 22 percent in 1952, to 60 percent by 1962 and may become much higher.⁵⁹

In the process of revealing ever larger numbers of early cancers of the cervix, cytology has also uncovered a spectrum of borderline lesions varying from benign to malignant. It is this gradation that is the source of a number of new problems in medical practice involving both the recognition and treatment of these various entities.

What is Carcinoma In Situ Of the Uterine Cervix?

Many of the clinical problems and controversies could be solved if all observers agreed on the significance of carcinoma *in situ*. The lesion was first described in 1888,¹⁰⁶ and is defined most simply as surface reaction, with or without gland or cleft²³ involvement, histologically identical with invasive carcinoma except for the absence of stromal invasion. It was not until recent years that opinion

crystallized to where it is generally agreed that carcinoma *in situ* is cancer; and that, untreated, it will eventually result in clinical cancer.¹⁰⁶ However, there are many observers^{11,31,33,53} who feel that correlation of the microscopic appearance and the ultimate outcome of the lesion is poor. These workers estimate that 10 to 60 percent of these lesions become invasive after a lag period of one to twenty years, while the remainder regress or are static during this time interval. This uncertainty as to whether a given lesion is irreversible caused the International Congress of Obstetrics and Gynecology in 1950 to place carcinoma *in situ* in a special group termed Stage 0 in the International Classification of cancer of the uterine cervix.⁵⁴

The main problem is to identify those atypias that are destined to become invasive, but there are a number of factors that make difficult the correlation of the histological appearance and clinical behavior of the lesions.

First, since microscopic diagnosis is subjective, there may be variations in the interpretation of the same lesion by different observers. This was shown strikingly by Siegler in 1956⁹⁵ when he submitted 20 slides of borderline lesions to 25 eminent pathologists and no two pathologists agreed on the diagnosis in all cases. His repeat study in 1961⁹⁶ showed that certain patterns of atypia were diagnosed rather consistently, though the average participating pathologist still placed five of twenty-five slides (20 percent) in the group labelled "Borderline, diagnosis uncertain." McGarrity in 1966⁶⁵ reported a similar study in which the slides of 71 cases with a previous diagnosis of carcinoma *in situ* were reviewed by three additional pathologists. There was a 65 percent confirmation of the original diagnosis, 28 percent were regarded as benign, and 7 percent were regarded as invasive. The trend has been to establish more rigid criteria by international agreement¹⁰⁴ but it is evident that the true significance of those lesions labeled as "carcinoma *in situ*" depends on the observer's critical level for making the diagnosis.³⁶

Second, certain lesions may have close histological and physico-chemical resemblance to cancer and yet are apparently completely unrelated. This is exemplified by the effect of podophyllin^{49,50} and silver nitrate⁴³ on the human cervix.

Third, prospective studies^{47,53,82} to evaluate clinical behavior are almost impossible, since the very process of biopsy tends to destroy some lesions. However, it is noteworthy that in Petersen's⁸²

series of 127 untreated patients with carcinoma in situ, 4 percent showed invasion after one year, 22 percent by five years and 33 percent by nine years. In other words, 67 percent of the lesions were either cured by biopsy, were not true carcinoma, or required more time to become so. Koss⁵³ pointed out that his studies show that no prognostic trend can be based on microscopic appearance. He further noted that carcinoma in situ is very fragile and may be readily eradicated by a variety of minor procedures. More, its natural course may be profoundly modified by excision of even small amounts of tissue for biopsy, by drugs, and possibly by physiological trauma such as delivery.

Fourth, carcinoma in situ may be multicentric in space or time. It is now recognized that Cohnheim's theory of unicentric origin of neoplasms is no longer tenable and the concept of a cancerogenic field or "sexual skin" has been advanced.⁷⁶ If a neoplastic lesion appears at one point in this field, it is possible that sooner or later this same process may start in another part of this field.^{40,48,67} This underlines the importance of follow-up, regardless of the treatment applied to the primary lesion.

Fifth, there are variations in the morphogenesis of clinical carcinoma. Invasive carcinomas do not all necessarily pass through an in-situ stage^{6,84,91} and some investigators believe that carcinoma in situ may not be a single entity.⁵ This bears on the relationship between clinical carcinoma and carcinoma in situ and on the usefulness of cytological screening for early detection of the tumor.

Despite these uncertainties in our understanding, the failure to correlate structure with clinical behavior does not completely discredit the concept of carcinoma in situ. The limitations must be recognized, but the fact remains that there is a clearly significant relation or association, even though obscure, between invasive carcinoma and carcinoma in situ (including certain other imprecisely defined dysplasias).^{6,31,53}

How Often and at What Age Should Smears be Taken?

In the early wave of enthusiasm for smears as a routine screening test, some workers advocated the test be performed every six months; but in recent years the majority opinion seems to have settled on obtaining the smear annually. This is usually a part of a general physical "checkup"; and, if the smear is not taken annually, the patient often asks

why not? However, periodic cytological examinations yield diminishing returns in a given group of patients.^{14,44,92} In the Louisville screening,¹⁴ after the third year, there was no case of invasive cervical cancer among those screened annually, and a steady rate of one carcinoma in situ for every 2,000 women screened over an eight-year period. Since the natural history of in situ carcinoma¹⁰⁶ indicates that most, if not all, of the lesions have a very slow evolution, a year or two should not make any difference in the clinical outcome. Consequently, in the patient with two or three negative smears at annual intervals, lengthening the interval between smears to two years will not increase appreciably her risk, if pelvic examination is done at the same time.^{64,92,105}

The age at which initial routine smears should be obtained was debated for some time, and arbitrary limits of age 30 and even age 20 were suggested. Studies^{13,15,20} now reveal that abnormal smears may be found at almost any age and cytological examination is indicated at the onset of a patient's sexual activity rather than a specific year.¹⁰⁵ Vaginal smears are indicated also in all pregnant women, since the prevalence rate of in situ carcinoma is similar to that in non-pregnant women, while pregnancy has no effect on the accuracy of the cytological examination.⁸⁵

How Accurate is the Smear?

There are a number of technical problems concerned with smears^{42,99} about which the clinician should constantly remind himself. He should remember that the vaginal smear is not perfect, and that false positive and false negative reports may occur for a number of reasons. The accuracy of the smear is dependent on the combined efforts of the clinician, technician, cytologist and patient. Proper technique in obtaining the smear is essential to proper interpretation; but, even so, a negative smear does not exclude carcinoma. False negative smears are known to occur in 10 to 31 percent of initial smears in patients subsequently shown to have in situ carcinoma of the cervix,^{32,52,97} but by using a combination of sampling methods much greater accuracy can be obtained.¹⁰³ Colposcopy may be used as a supplementary method to increase accuracy of initial diagnosis⁵²; but, in the United States, this procedure is believed generally to be impractical in daily clinical work.⁴¹ However, some observers would use it after the patient has been cytologically screened, for the per-

formance of adequate "guided" excision of biopsy material in the clinic or office.^{8,51,52,97}

Good communication and a mutual understanding of the nomenclature by all parties are vital. This permits the clinician to estimate the likelihood of any given smear indicating carcinoma, and provides the basis for a more realistic management of the patient. One should familiarize himself with the philosophy of the laboratory facility he is using, and then never try to apply it to any other laboratory.⁶¹

How is the Diagnosis Established?

It is generally agreed that a cytologic smear suspicious for malignant change should not be used as a basis for treatment. In such event it is wise to repeat the smear (especially if there is no visible lesion) in order to avoid treating a false-positive condition, but the cause of a persistently atypical smear must be evaluated by adequate biopsy. Adequate biopsy is one which can with reasonable certainty establish or exclude the presence of invasion, since carcinoma in situ and invasive carcinoma may co-exist.

Multiple punch biopsy, especially of iodine non-staining areas, can be reliable when combined with endocervical curettage.^{16,100,105} This is a relatively simple office procedure, and may save time and expense if invasion is demonstrated. In addition the procedure may be used to advantage during pregnancy, for it can exclude grossly invasive cancer and yet avoid the possible complications of cone excision of sufficient material for accurate evaluation of a questionable lesion.^{46,87} A superficial cone biopsy during pregnancy reduces the risk of complications, but seems to have little advantage over properly performed multiple punch biopsy.⁶⁹ Finally, the procedure may be used to advantage in the young nullipara, whose reproductive potential might be compromised by a deep cone excision of biopsy material.³⁴

Cold-knife conization is generally recognized as the more accurate method for establishing the diagnosis of non-invasive cancer.² The techniques may vary but the basic principles were detailed by Scott and Reagan⁹³: These include delineation of the excision area by iodine staining, then free-hand excision so as to remove all the unstained zone plus a narrow border of stained tissue, including at least 1.5 cm of intact cervical canal in the cone, and performing fractional curettage *after* removal of

the cone. These dimensions of an adequate cone biopsy are confirmed by the studies of Pryzbora.⁸³ Using a similar method of conization, Silbar⁹⁷ in 185 cases of punch biopsy followed by cone biopsy found 11 instances of invasive carcinoma not recognized in the punch biopsy but discovered in the cone material, an error of close to 6 percent. Villasanta¹⁰² found the cone more effective than punch biopsy in making the correct diagnosis in 32 percent of his cases, but Dilts¹⁶ reported inadequate diagnosis by punch biopsy in only 2.5 percent of 244 patients.

While cone biopsy may be more accurate in the hands of the average clinician, it is not an innocuous procedure when an adequate amount of tissue is removed. In addition to the need for the patients to enter a hospital and have anesthesia, there are the annoying and sometimes dangerous complications of post-conization hemorrhage and infection. Hemorrhage of that kind occurred in 10 percent of 200 consecutive cases in which cone biopsy was done.¹⁰² Twenty-two methods of conization were used, and yet hemorrhage occurred slightly more often when post-conization packing was used. Mattress sutures (preferably non-absorbable) may reduce the incidence of bleeding, particularly when left in place through the following menstrual period.⁹⁸ However, despite all attempts at prophylaxis, delayed heavy bleeding may occur which can be extremely difficult to control; and there is occasional resort to hysterectomy with possibly disastrous results from sepsis.^{12,62} A safer method of controlling delayed hemorrhage is by local non-absorbable sutures; or, this failing, by internal iliac ligation.⁵⁸

Post-conization infection may be most serious when hysterectomy is performed soon after cone biopsy has revealed carcinoma in situ. Studies relating morbidity and mortality rates to the time interval between cone biopsy and hysterectomy showed that the rates were highest when hysterectomy was performed between the third to the eighteenth post-conization day.^{12,62} Consequently, hysterectomy should be either performed within 48 hours of conization, or delayed until healing of the cervix is complete—about four to six weeks.^{73,93} Careful study of the cone specimen is more important to the patient than immediate hysterectomy¹²; and Morton⁷³ pointed out that, taking all things on balance, the better method is to allow the cervix to heal and perform hysterectomy six weeks later.

How Should Cervical Carcinoma In Situ Be Treated?

Ferguson¹⁹ said that there are large groups of women with positive smears in whom *frank* malignant change does not exist and the management of these patients looms as the newest challenge gynecology has to meet. In view of the wide range of histological findings in Stage 0 cervical carcinoma, no single treatment is ideally suited for all lesions. Treatment is influenced by our understanding of the significance of these lesions: that there is never a sudden change from in situ to invasive carcinoma, that we cannot correlate well the histological appearance and the clinical behavior of the condition, and that these lesions—in contrast to invasive carcinoma — are easily destroyed.^{11,53} Thus, fear of carcinoma in situ should not force us to hasty over-treatment.^{1,33,105}

There is no question that treatment is indicated in all cases of cervical atypism, but the problem is: *how much treatment?* This uncertainty is due to the existence of two zones of controversy in the histologic diagnosis of early cancer²⁴: first, the differentiation of dysplasia from carcinoma in situ; and, second, the precise distinction between carcinoma in situ, and minimally ("early") invasive carcinoma. Dysplasia is considered clinically a benign lesion, although Richart⁸⁶ reported progression to carcinoma in situ in approximately 25 percent of 520 cases. Also, dysplasia may co-exist with invasive carcinoma.⁶⁶ Consequently, it is best to treat dysplasia when it is detected. This may be accomplished adequately by the cold-conization necessary for accurate diagnosis, if followed by regular cytological examinations.^{69,94}

Two Plans of Treatment

In the presence of carcinoma in situ, there are two plans of treatment: first, the treatment favored by most observers, consisting of the extra-fascial

hysterectomy together with removal of 1 to 2 cm of the vaginal vault^{37,70,94}; and, second, the so-called conservative or graded approach to treatment by conization and follow-up smears.^{10,33,52,56,68,90} In attempting to evaluate the effectiveness of any treatment for carcinoma in situ of the cervix, it is conceded generally that postoperative cytologic examination is the single most important test. On the basis of this examination, a "persistent" or "residual" lesion is inferred when the first postoperative smear is positive; and "recurrence" is implied when the smears become positive after one or more postoperative smears have been negative.⁶⁸ However, it has been shown that many patients have positive smears in the post-biopsy healing phase which subsequently become negative; so that "persistent" or "residual" disease should not be inferred unless follow-up smears are still positive six months after local excision, always providing that review of the first biopsy shows no frank invasion.^{33,56}

The Arguments for Hysterectomy

Proponents of hysterectomy for the treatment of carcinoma in situ believe that the constant follow-up required with the conservative treatment plan is not justified for the patient whose family is complete, and that the risk of progression of the lesion to invasive carcinoma justifies the greater risk of the major operation in the belief that hysterectomy is "definitive" treatment. Yet, in young patients exceptions are made for the preservation of reproductive potential. Reviews of collected series of hysterectomy for in situ carcinoma reveals residual or persistent disease in 8 percent to 50 percent of the hysterectomy specimens after conization,³⁰ the incidence in part being related to the adequacy of the conization and the care used in the study of the specimens. These series reveal also a variable but definite recurrence of carcinoma in situ in the vaginal vault³⁷ and pos-

TABLE 1.—Recurrence after Treatment of Carcinoma In-Situ of the Uterine Cervix by Total Hysterectomy

Reported by author & year		Follow-up (years)	No. of in-situ cases treated	Persistence	Late recurrence in-situ	invasive	Time invasive cancer discovered after treatment
Mussey ⁷⁴	1959	2-23	721	..	2	3	3 yr; 5 yr; 10 yr
Parker ⁸⁰	1960	1-13	300	1	1	1	4½ yr
Beecham ⁷	1962	1-10	131	..	2	3	2½ yr; 5 yr; 10 yr*
Gusberg ³⁷	1962	1-20	240	..	2	0	
Funnell ²⁷	1963	1-6	73	1	3	1	3 yr
Giglio ²⁸	1965	1-6	98	..	.	1	20 months
Lyon ⁶⁰	1965	1-5	100	
Kolstad ⁵²	1966	2-15	106	1	1	2	3 yr; 6 months
Totals			1769	3	11 (0.62%)	11 (0.62%)	

*Recurrence in lower vagina.

sible later development of changes in the remaining squamous epithelial field.^{3,45} This is also shown in Table 1. Persistence of the disease in the vagina was almost nil, but late recurrence in the vagina amounted to 1.24 percent. Surprisingly, half of the recurrent lesions were invasive tumors, the majority of which were discovered three or more years after the "definitive" treatment. These might have been detected in the pre-invasive stage by regular follow-up. It is apparent that hysterectomy is an excellent but not always "definitive" method of treatment for in situ carcinoma, and does not obviate the need for regular surveillance after operation.¹⁰

The Graded Approach

The conservative or graded approach to the treatment of carcinoma in situ of the cervix is well outlined by Krieger.⁵⁷ Histological examination is necessary for diagnosis, but exfoliative cytology is the major technique for detection and for assessing the effectiveness of treatment. This presupposes a patient who can cooperate in proper follow-up and a clinician who does not believe that hysterectomy is necessarily a good form of psychotherapy. The physician must have the knowledge and ability to explain the facts about incipient cancer of the cervix in such a manner that the patient understands that her life or health is not threatened.³⁸ After the diagnosis is established by cone biopsy and curettage, if no invasion is demonstrated, and even in those cases where the in situ lesion extends to the margin of the specimen,^{10,33} the cervix is permitted to heal and follow-up smears obtained in six weeks, then three months later and six months after that. Thereafter, smears are obtained yearly. Thus, one year after conization the patient follows the optimal schedule of examinations suggested for any woman with an intact cervix. If the conization fails to control the carcinoma in situ, there will be cytologic evidence in the first two studies after the cone; and repeat conization or hysterectomy is done. If cervical

stenosis develops or other pelvic disease is present, then vaginal or abdominal hysterectomy is carried out. This approach to the treatment exposes fewer patients to the risks of major operation and avoids hysterectomy in the immediate post-conization period. In addition, it avoids the over-treatment of the lesser dysplasias and is calculated to control the disease in accordance with its clinical behavior.

No single large series of patients with long follow-up after treatment by conization has been reported, for this method has been used by few observers and for not much more than 15 years.⁸¹ Further, in any given series of patients with carcinoma in situ, conization is not the only treatment used. However, several series of 100 or more cases have been reported (Table 2) and in this total of 1,101 patients with carcinoma in situ treated by conization, there was 2.3 percent persistence and 3.5 percent late recurrence—both events dealt with successfully by repeat conization or hysterectomy. There was but one case of recurrence with invasion, and this responded to radiation. Table 2 indicates that more than 90 percent of cases of carcinoma in situ may be controlled by conization, and that the graded approach to treatment may be used safely to control the disease. In this way, the clinical behavior of the lesion will determine therapy, and considerations of age, parity and future reproductive potential carry no real weight in decisions as to desirable or safe treatment in a given patient.⁵⁷ The increasing confidence of clinicians in their ability to control carcinoma in situ by local excision is underlined by reports from other countries: in New South Wales,⁶⁵ from 1955 to 1964, the use of conization as sole treatment increased from 3 percent to 30 percent; while at the Norwegian Radium Hospital⁵² from 1950 to 1963, its use as sole treatment increased from 4.5 percent to 68 percent.

In Situ, or Minimally Invasive?

At the other end of the spectrum of cervical atypism is the second zone of controversy involving the precise distinction between carcinoma in situ

TABLE 2.—*Recurrence after Treatment of Carcinoma In-Situ of the Uterine Cervix by Conization*

<i>Reported by author & year</i>	<i>Follow-up (years)</i>	<i>No. of in-situ cases treated</i>	<i>Persistence</i>	<i>Late recurrence in-situ</i>	<i>invasive</i>	<i>Time invasive cancer discovered after treatment</i>
Krieger ⁵⁶	1963	1-12	197	9	0	1
Michalkiewicz ⁶⁸	1963	1-8	368	8	7	0
Green ³³	1966	1-15	288	9	26	0
Kolstad ⁵²	1966	2-15	248	0	4	0
Totals		1101	26 (2.3%)	37 (3.4%)	1 (0.1%)	

*Positive smear two months after conization. Did not return for two years. Irradiated and well.

and minimally invasive carcinoma together with the problem of the treatment of predominantly in situ lesions containing areas of minimal stromal invasion. This finding occurs in about 5 to 10 percent of otherwise predominantly in situ lesions, although the incidence is reported as high as 60 percent in some series.¹⁰¹

There are many clinicians who feel that once invasion is demonstrated, no matter how minute, the patient must be treated fully as clinical Stage I. There are others^{17,33,55,63,70,73,88} who feel that these borderline lesions can be treated safely by less radical measures. The difficulty is to define the group that can be so treated.

Pathologists for some time have described gradations from in situ carcinoma, to questionable invasion, to foci of microinvasion and finally the confluence of such foci to form minute but typically invasive carcinoma.^{21,22,24,84} Some clinics have elected to include cases of questionable stromal invasion in Stage I carcinoma of the cervix while others retain this lesion in Stage 0.²⁶ On the other hand, in cases of in situ lesions with isolated but definite tongues of invasion, some clinics place these in Stage 0 for treatment purposes,^{24,70} while others retain them in Stage I and treat them as such.

The world congress of the International Federation of Obstetrics and Gynecology in 1961 took note of the increasing number of early lesions being reported and accepted a subdivision of Stage I carcinoma of the cervix into Stage Ia to include "cases of early stromal invasion (preclinical carcinoma)" and Stage Ib for "all other cases of Stage I." A footnote to the definition points out: "A case should be allotted to Stage Ia only following microscopic diagnosis of the earliest stromal invasion performed before planned treatment. Stage Ia represents that group of cases of carcinoma of the cervix which can only be diagnosed microscopically following biopsy. They have often formerly been called micro-carcinoma. In the remainder of Stage I cases a clinical diagnosis will be possible."⁵⁴ However, this definition of Ia includes frank but "occult" carcinomas as well as the borderline lesions in question, and is too broad to aid in the study of the most minimal lesions.

In an attempt to define these borderline lesions more precisely, microinvasion or minimal stromal invasion has been described as predominantly carcinoma in situ but with isolated tongues of invasion to a depth of 3 to 5 mm.^{24,70} A less arbitrary

definition was made by Ullery,¹⁰¹ who defined microinvasive carcinoma as identical to carcinoma in situ with an additional small discrete focus or foci of invasion beyond the limiting basement membrane; but, in addition: (1) these microscopic foci do not extend more than 3 to 4 mm into the underlying stroma, (2) there is no evidence of lymphatic permeation and (3) there is no evidence that these microscopic foci coalesce, as they quite frankly do in invasive carcinoma. Margulis⁶³ defined microinvasion similarly but considers the lesion synonymous with Stage Ia. Fidler²¹ has also emphasized the significance of confluent foci of invasion.

The importance of the distinction between these early stages of invasion is one of prognosis. These earliest stages of carcinoma of the cervix have much higher cure rates (97 percent to 99 percent five-year survivals) than do clinically apparent Stage I lesions,⁸⁸ and we may be led into false complacency with our results of treatment, while paying too high a price in patient morbidity and mortality. The validity of these distinctions is indicated by the fact that lymph node metastasis rarely occurs in minimal stromal invasion^{9,18,25} and that this remote risk is balanced by the small but appreciable immediate and late surgical mortality of the radical hysterectomy with node dissection, not to consider the occasional serious complications of radical operation and irradiation. Further, Przybora⁸⁴ stated that investigations in recent years have shown that cancer with incipient stromal invasion has its individual biologic character, and that therapy should be different from that applied to frankly invasive cancer. Finally, Glucksmann and Cherry,²⁹ in discussing the histopathological aspects of microinvasive carcinoma of the cervix, said that the use of the term "invasive" cancer and its distinction from the less malignant "non-invasive" or "in situ" condition fails to draw attention to the fact that, as in embolic spread of tumors, invasive-like foci may not have the ability to grow in their new surroundings—that is, xenotopically.

The conditions of carcinoma in situ with questionable invasion of stroma, and carcinoma in situ with definite but minimal invasion, both resemble carcinoma in situ as regards inability of xenotopic growth. Glucksmann and Cherry pointed out that it is not yet possible to base a diagnosis of micro-carcinoma on specific changes in ultra-structure, histochemistry or chromosomal compositions of its cells. However, we can distin-

TABLE 3.—Recurrence after Non-Radical Treatment of Minimally Invasive Carcinoma of the Cervix Uteri

Reported by Author	Year	Follow-up (years)	No. of cases treated	Treatment Method			Recurrence		
				extrafascial hysterectomy	coniza- tion	radium only	in- situ	invasive	metastases
Ullery ¹⁰¹ (collected series)	1965	5 or more	242	242			0	0	0
Przybora ⁸⁴	1965	1-8	67	61	6		0	0	0
Kottmeier ⁵⁵	1965	3-6	132			132	0	0	0
Green ³³	1966	1-7	40		40		3*	0	0
Margulis ⁶³	1967	1-8	11	11			0	1**	0
Totals			492	314	46	132	3	1	0

* 3 positive smears 1 to 4 years after conization. All re-treated and well.

** 1 microinvasive (vagina) 5 years later. Re-treated and well.

guish between microinvasive carcinoma and other stages of carcinogenesis by noting, on the one hand, invasion *without* evidence of growth of the invading foci; and, on the other hand, noting invasion *with* evidence of proliferation of the invading foci. Like carcinoma in situ, the microcarcinoma is unlikely to "spread"—that is, to lead to a dissemination of growing foci in new surroundings.

Clinical evidence for the safety of less radical methods in the treatment of minimally invasive carcinoma is slowly accumulating. Ullery¹⁰¹ collected from the literature more than 200 cases of microinvasive carcinoma treated by hysterectomy without pelvic lymphadenectomy. The five-year survival rate was close to 100 percent and there were no deaths due to tumor metastasis in this group. Table 3 includes some recent additional reports on the non-radical treatment of minimally invasive lesions. While lengths of follow-up still leave something to be desired, it is noteworthy that in almost 500 cases no death occurred from treatment and the solitary recurrence was a microinvasive lesion in the vagina.

What the proper treatment is for these minimally invasive lesions is still not settled, but it is essential that treatment decisions be based on careful study of an adequate biopsy specimen by a competent pathologist; and that nomenclature and definitions be precise. If any degree of invasion is present, then by definition⁵⁴ the lesion is to be included in Stage Ia. However, treatment may be individualized just as it is in more advanced stages of the disease. It is at this point that every physician treating carcinoma of the cervix must establish his own code for relating extent of treatment to degree of invasion; but, regardless of what treatment is chosen, these minimal lesions deserve a special category for further study.^{21,24}

How Shall Carcinoma In Situ Found During Pregnancy be Managed?

Carcinoma in situ of the cervix associated with pregnancy is being found with increasing frequency as routine vaginal smear screening is done in more and more gravid women. Several recent papers on the subject^{71,75,78} provide an excellent review of the literature and chronicle the evolution of present concepts in the diagnosis and management of this increasingly frequent clinical problem.

Pregnancy does not impair the accuracy of the smear in detecting in situ lesions, nor the validity of the histological diagnosis of such lesions.^{35,85} The behavior of the lesions in pregnancy is similar to that in women who are not pregnant, but in a small proportion of cases they do not persist post-partum, perhaps being destroyed by the process of delivery.⁵³

The basic principle in the management of abnormal smears in pregnancy is the same as in the non-pregnant state—that is, to make sure that there is not a co-existing invasive carcinoma. Most reports indicate a preference for cone biopsy of the cervix despite pregnancy, but with preference for carrying out the procedure after the first trimester and before the last four weeks of gestation.^{75,78} The cone removed is not as extensive as would be taken in other circumstances, lest the procedure cause abortion, premature labor or severe hemorrhage. Because of this, there are investigators^{46,69,87,105} who believe that multiple punch biopsy combined with endocervical curettage is equally accurate and less dangerous. Multiple biopsy is used by most clinicians when the cervix is decidedly lacerated and hypertrophied, and also during the last four weeks of pregnancy.

If tissue studies reveal no more than a minimally invasive (not frankly infiltrative) lesion,^{71,78} then

the pregnancy is allowed to continue and vaginal smears are repeated every six weeks. Vaginal delivery is permitted unless obstetric complications interfere. Reevaluation begins with repeat smears at six weeks postpartum with repeat punch biopsy or conization as indicated and hysterectomy if necessary. Moore⁷¹ reported that in one-third of the cases in which cone biopsy was done during pregnancy, the procedure did not clear the lesion; hence these patients should have a repeat of conization even in the presence of normal smears. Ullery¹⁰¹ urged postpartum repeat cone biopsy before definitive treatment as the less extensive removal of tissue by conization during pregnancy might have permitted a microinvasive carcinoma to escape detection. This could result in less than ideal therapy for such a lesion if the proper therapy for it is considered to be more than a simple hysterectomy.

Conclusion

This review has attempted to discuss some of the clinical problems raised by the increased use of the vaginal smear and our increased ability to make an early diagnosis of cancer of the cervix. The resulting decrease in death rate from the disease does not always reflect the cost of treatment in terms of post-operative hemorrhage, infection, fistulas and death. These post-operative complications are even more tragic when the hysterectomy specimen shows no residual cancer. If we focus attention on these border-line lesions, better understand their clinical behavior, and increase our precision in diagnosis, we shall be better able to individualize therapy and obtain a more perfect result for a given patient.

REFERENCES

- Adelman, H. C., and Hajdu, S. I.: Role of conization in the treatment of cervical carcinoma in situ, *Amer. J. Obstet. Gynec.*, 98:173-179, May 15, 1967.
- Anderson, S. G., and Linton, E. B.: The diagnostic accuracy of cervical biopsy and cervical conization, *Amer. J. Obstet. Gynec.*, 99:113-116, Sept. 1, 1967.
- Ashe, J. R., Arey, J. V., and Williams, J. O.: The abnormal cytological smear, *Amer. J. Obstet. Gynec.*, 87:320, Oct. 1, 1963.
- Ashley, D. J. B.: The biological status of carcinoma in-situ of the uterine cervix, *J. Obstet. Gynaec. Brit. Comm.*, 73:372-381, June, 1966.
- Ashley, D. J. B.: Evidence of the existence of two forms of cervical carcinoma, *J. Obstet. Gynaec. Brit. Comm.*, 73:382-389, June, 1966.
- Bangle, R., Jr., Boyer, M., and Levin, J.: Variations of the morphogenesis of squamous carcinoma of the cervix, *Cancer*, 16:1151, Sept. 1963.
- Beecham, C. T., Carlin, E. S.: The management of cervical carcinoma in situ, *Assn. New York Acad. Sc.*, 97:814-820, Sept. 29, 1962.
- Beller, F. K., and Khatamee, J.: Evaluation of punch biopsy of the cervix under direct colposcopic observation (Target punch biopsy), *Obstet. Gynec.*, 28:622-625.
- Beyer, F. D., Jr., and Murphy, A.: Patterns of spread of invasive cancer of the uterine cervix, *Cancer*, 18:34-40, Jan., 1965.
- Boyd, J. R., Doyle, D., Fidler, H. K., Boyes, D. A.: The conservative management of in situ carcinoma, *Amer. J. Obstet. Gynec.*, 85:322-327, Feb. 1, 1963.
- Boyes, D., Fidler, H. K., and Lock, D. R.: Significance of in situ carcinoma of the uterine cervix, *Brit. Med. J.*, 1:203-205, Jan. 27, 1962.
- Cavanagh, D., and Rudledge, F.: The cervical cone biopsy—hysterectomy sequence and factors affecting the febrile morbidity, *Amer. J. Obstet. Gynec.*, 80:53-59, July, 1960.
- Cavanagh, D., McLeod, A. G. W., and Ferguson, J. H.: Carcinoma of the cervix among women in their twenties, *JAMA*, 195:834-836, Mar. 7, 1966.
- Christopherson, W. M., Parker, J. E., and Drye, J. C.: Control of cervical cancer. Preliminary report on community program, *JAMA*, 182:179-182, Oct. 13, 1962.
- Christopherson, W. M.: Risk of cervical cancer in teen-aged girls, *JAMA*, 194:196-197, Oct. 11, 1965.
- Dilts, P. V., Elesh, R. H., and Greene, R. R.: Re-evaluation of 4 quadrant punch biopsies of cervix, *Amer. J. Obstet. Gynec.*, 90 (part 1):961-971, Dec. 1, 1964.
- Dilworth, E. E., and Maxwell, G. E.: Superficial invasive carcinoma and carcinoma in situ of the uterine cervix, *Amer. J. Obstet. Gynec.*, 84:83-88, July 1, 1962.
- Enterline, H. T.: Management of microinvasive carcinoma, *JAMA*, 193:220-221, July 19, 1965.
- Ferguson, J. H., and Offen, J. A.: Management of women with positive vaginal cytological findings, *JAMA*, 170:1892-1895, Aug. 15, 1959.
- Ferguson, J. H.: Positive cancer smears in teenage girls, *JAMA*, 178:365-368, Oct. 28, 1961.
- Fidler, H. K., and Boyes, D. A.: Patterns of early invasion from intraepithelial carcinoma of the cervix, *Cancer*, 12:673-680, July-Aug., 1959.
- Fidler, H. K., and Boyd, J. R.: Occult invasive squamous carcinoma of the cervix, *Cancer*, 13:764-771, July-Aug., 1960.
- Fluhmann, F.: Involvement of clefts and tunnels in carcinoma in situ of the cervix uteri, *Amer. J. Obstet. Gynec.*, 83:1410-1421, June 1, 1962.
- Frick, H. C., Janovski, N. A., Gusberg, S. B., and Taylor, H. C., Jr.: Early invasive carcinoma of the cervix, *Amer. J. Obstet. Gynec.*, 85:926-939, Apr. 1, 1963.
- Friedell, G. H., and Graham, J. B.: Regional lymph node involvement in small carcinoma of the cervix, *Surg. Gynec. Obstet.*, 108:513-517, May, 1959.
- Friedell, G. H.: Premalignant lesions of the cervix, *Clin. Obstet. Gynec.*, 5:1127-1136, Dec., 1962.
- Funnell, J. D.: Recurrence after treatment of carcinoma in situ of the cervix, *Surg. Gynec. Obstet.*, 117:15-19, July, 1963.
- Giglio, F. A., Dowling, E. A., and Jones, W. N.: Carcinoma in situ of the cervix, *Amer. J. Obstet. Gynec.*, 93:193-198, Sept. 15, 1965.
- Glückmann, A., and Cherry, C. P.: Microinvasive carcinoma of the cervix; Histopathological aspects; *From Dysplasia, Carcinoma in situ and Micro-invasive Carcinoma of the Cervix Uteri*, compiled by Laman A. Gray, Charles C Thomas, Springfield, Ill., 1964, Chap. 15.
- Gough, H. M.: Treatment of intraepithelial carcinoma of the cervix, *Canad. Med. Ass. J.*, 86:974-976, May 26, 1962.
- Graham, J. B., Sotto, L. S., and Poloncek, F. P.: Carcinoma of the Cervix, W. B. Saunders Company, Philadelphia, 1962, Chapter 4.
- Graham, R. M., Meigs, J. V.: The value of the vaginal smear, *Amer. J. Obstet. Gynec.*, 58:843-850, Nov., 1949.
- Green, G. H.: The significance of cervical carcinoma in situ, *Amer. J. Obstet. Gynec.*, 94:1009-1022, Apr. 1, 1966.
- Green, G. H.: Pregnancy following cervical carcinoma in situ, a review of 60 cases, *J. Obstet. Gynaec. Brit. Comm.*, 73:897-902, Dec. 1966.
- Green, R. R., and Packham, B. M.: Pre-invasive cancer of the cervix and pregnancy, *Amer. J. Obstet. Gynec.*, 75:551-564, Mar., 1958.
- Gross, S. J.: Current problems in the laboratory diagnosis of cervical cancer, *Amer. J. Obstet. Gynec.*, 82:449-455, Aug., 1961.
- Gusberg, S. B., and Marshall, D.: Intraepithelial cancer of the cervix: A clinical reappraisal, *Obstet. Gynec.*, 19:713-720, June, 1962.
- Gusberg, S. B.: Treatment of carcinoma in situ of the cervix, the role of hysterectomy, *Postgrad. Med.*, 35:128-131, Feb., 1964.
- Hammond, E. C., and Seidman, H.: Uterine cancer control—success and challenge, *Obstet. Gynec. News*, 1:1, Nov., 1966.
- Hansen, L. H., and Collins, C. G.: Multicentric squamous cell carcinoma of the lower female genital tract, *Amer. J. Obstet. Gynec.*, 98:892-896, Aug. 1, 1967.
- Hill, E. C.: Preclinical cervical carcinoma, colposcopy and the "negative smear," *Amer. J. Obstet. Gynec.*, 95:308-319, June 1, 1966.
- Horton, R.: Cervical-vaginal smears cytologic examination, *Calif. Med.*, 104:366-367, May, 1966.
- Hulka, J. F., and Ison, A.: Cervical dysplasia associated with silver nitrate cauterization, *Amer. J. Obstet. Gynec.*, 90:1361-1362, Dec. 15, 1964.
- Hulka, B. S.: Detection of cervical cancer among the medically indigent, *Public Health Rep.*, 81:143, Feb., 1966.

45. Isaacs, J. H., and O'Connor, J. S.: Recurrent carcinoma in situ of the cervix, *Obstet. Gynec.*, 25:356-361, Mar., 1965.
46. Jones, E. G., Varga, A., Leff, J. G., Schwinn, C. P., Slate, W. G., Wargin, J. T., and Bullock, W. K.: Efficiency of multiple biopsy for cancer detection during pregnancy: A progress report, *Obstet. Gynec.*, 26:70-76, July, 1965.
47. Jordan, M. J., et al: Carcinoma in situ of cervix and related lesions: an 11 year prospective study (of 379 patients with cervix lesions): *Amer. J. Obstet. Gynec.*, 89:160, May 15, 1964.
48. Julian, C. G., and Woodruff, J. D.: Multiple anaplasias in the lower genital canal, *Amer. J. Obstet. Gynec.*, 95:681-691, July 1, 1966.
49. Kaminetzky, H. A.: Human cervical epithelial changes produced by podophyllin, *Amer. J. Obstet. Gynec.*, 80:1055-1062, Dec., 1960.
50. Kaminetzky, H. A., and McGrew, E. A.: The effect of podophyllin on the human endocervix, *Obstet. Gynec.*, 18:255-258, Sept., 1961.
51. Kaufmann, William: The use of colposcopy in a cancer screening program, *Acta Cytol.*, 9:395-396, Sept.-Oct., 1965.
52. Kolstad, P.: Carcinoma of the cervix, Stage 0—diagnosis and treatment, *Amer. J. Obstet. Gynec.*, 96:1098-1111, Dec. 15, 1966.
53. Koss, L. G., Stewart, F. W., Foote, F. W., Jordan, M. J., Bader, G. M., and Day, E.: Some histologic aspects of behavior of epidermoid carcinoma in situ and related lesions of uterine cervix: Long term prospective study, *Cancer*, 16:1160-1211, Sept., 1963.
54. Kottmeier, H. L., editor: Annual report on the results of treatment in carcinoma of the uterus and vagina: Statements of results obtained in 1948 to 1957, inclusive, Published under the patronage of the International Federation of Gynecology and Obstet., Stockholm, Sweden, 13, 1965.
55. Kottmeier, H. L.: Questionable early stromal invasion and minimal invasive cervical carcinoma, *J. Int. Fed. Gynec. Obstet.*, 3:3-12, 1965.
56. Krieger, J. S., McCormack, L. J., and Bradley, V. F.: The role of conization in the detection and treatment of cervical carcinoma in situ, *Amer. J. Obstet. Gynec.*, 86:120-129, May 1, 1963.
57. Krieger, J. S.: Conservative treatment of carcinoma in situ of uterine cervix, *Postgrad. Med.*, 35:124-127, Feb., 1964.
58. LeCocq, F.: Internal iliac ligation, *Amer. J. Obstet. Gynec.*, 95:320-326, June 1, 1966.
59. Linden, G., and Dunn, J. E., Jr.: Earlier diagnosis of cervical cancer—an analysis of reports to the California Tumor Registry from 1942 to 1963, *Calif. Med.*, 105:331-336, Nov., 1966.
60. Lyon, J. B., Hajjar, S., and Thompson, D.: Vaginal hysterectomy and partial vaginectomy for carcinoma in situ of the uterine cervix, *Southern Med. J.*, 58:937-944, Aug., 1965.
61. Lyons, H. M.: Discussion of: The prevalence and significance of the Class II smear in the routine screening for detection of carcinoma of the cervix, *Amer. J. Obstet. Gynec.*, 92:642-649, July 1, 1965.
62. Malinak, L. R., Jeffrey, R. A., Jr., and Dunn, William J.: The conization-hysterectomy time interval, a clinical and pathologic study, *Obstet. Gynec.*, 23:317-329, Mar., 1964.
63. Margulis, R. R., Ely, C. W., Jr., and Ladd, J. E.: Diagnosis and management of State Ia (microinvasive carcinoma of the cervix, *Obstet. Gynec.*, 29:529-538, Apr., 1967.
64. Marshall, C. E.: How often should cervical Papanicolaou smear examination be made? *Med. J. Aust.*, 1:684-685, May 5, 1962.
65. McGarrity, K. A.: A review of intraepithelial carcinoma of the uterine cervix in New South Wales, *Aust. New Zeal. J. Obstet. Gynaec.*, 6:45-50, Feb., 1966.
66. McKay, D. G., Terjanian, B., Poschachinda, D., Younge, P. A., and Hertz, A. T.: Clinical and pathologic significance of anaplasia (atypical hyperplasia) of the cervix uteri, *Obstet. Gynec.*, 13:2-21, Jan., 1959.
67. McPherson, H. A., Diddle, A. W., Gardner, W. H., and Williamson, P. J.: Epidermoid carcinoma of the cervix, vagina and vulva: A regional disease, *Obstet. Gynec.*, 21:145-149, Feb., 1963.
68. Michalkiewicz, W., Przybora, L. A., Simm, S., and Wolna, M.: Recurrence and therapeutic problems in cervical dysplasia and in situ cancer, *Cancer*, 16:1212-1221, Sept., 1963.
69. Montgomery, J. B., and Long, J. P.: Diagnosis and management of cervical atypism, *Clin. Obstet. Gynec.*, 6:357-364, June, 1963.
70. Moore, J. G., Morton, D. G., Applegate, J. W., and Hindle, W.: Management of early carcinoma, *Amer. J. Obstet. Gynec.*, 81:1175-1181, June, 1961.
71. Moore, J. G., Wells, R. G., Morton, D. G.: Management of superficial cervical cancer in pregnancy, *Obstet. Gynec.*, 27:307-318, Mar., 1966.
72. Morton, D. G.: Early diagnosis and proper management in cervical cancer, *JAMA*, 118:271-273, Jan. 24, 1942.
73. Morton, D. G.: Incipient carcinoma of the cervix, *Amer. J. Obstet. Gynec.*, 90:64-72, Sept. 1, 1964.
74. Mussey, E., and Soule, E. H.: Carcinoma in situ of the cervix, a clinical review of 842 cases, *Amer. J. Obstet. Gynec.*, 77:957-972, May, 1959.
75. Mussey, E., and Decker, D. G.: Intraepithelial carcinoma of the cervix in association with pregnancy, *Amer. J. Obstet. Gynec.*, 97:30-38, Jan. 1, 1967.
76. Newman, W., and Cromer, J. D.: Multicentric origin of carcinomas of female anogenital tract, *Surg. Gynec. Obstet.*, 108:273-281, Mar., 1959.
77. Novak, Emil: What constitutes an adequate cancer detection examination of the cervix? *Amer. J. Obstet. Gynec.*, 58:851-866, Nov., 1949.
78. O'Leary, J. A., Munnell, E. W., and Moore, J. G.: The changing prognosis of cervical carcinoma during pregnancy, *Obstet. Gynec.*, 28:460-468, Oct., 1966.
79. Papanicolaou, G. N., and Traut, H. F.: *Diagnosis of Uterine Cancer by the Vaginal Smear*, Commonwealth Fund, New York, 1943.
80. Parker, R. T., Cuyler, W. K., Kaufman, L. A., Carter, B., Thomas, W. L., Creadick, R. N., Turner, V. H., Peete, C. H., and Cherney, W. B.: Intraepithelial (Stage 0) cancer of the cervix, *Amer. J. Obstet. Gynec.*, 80:693-710, Oct., 1960.
81. Peighal, T. C., Brandes, W. W., Crawford, D. B., and Dakin, E. S.: Conservative treatment of carcinoma in situ of the cervix, a clinical and cytopathologic study, *Amer. J. Obstet. Gynec.*, 69:547-552, Mar., 1955.
82. Petersen, Olaf: Spontaneous course of cervical precancerous conditions, *Amer. J. Obstet. Gynec.*, 72:1063-1071, Nov., 1956.
83. Przybora, L. A., and Plutowa, A.: Histological topography of carcinoma in situ of the cervix uteri, *Cancer*, 12:263-277, Mar.-Apr., 1959.
84. Przybora, L. A.: Incipient invasion of cervical cancer: Morphological aspects of carcinogenesis in 74 cases, *Gynaecologia*, 160:69-86 (No. 2), 1965.
85. Rad, M., Marczinke, I., Boyes, D. A., and Fidler, H. K.: The use of exfoliative vaginal cytology in pregnancy, *Amer. J. Obstet. Gynec.*, 94:465-470, Feb. 15, 1966.
86. Richart, Ralph M.: Significance of cervical dysplasia, *Med. Tribune*, 8:1, Apr. 17, 1967.
87. Rogers, R. S., and Williams, J. H.: The impact of suspicious Papanicolaou smear on pregnancy, *Amer. J. Obstet. Gynec.*, 98:488-496, June 15, 1967.
88. Roman, T. N., and Latour, J. P. A.: The effect of early diagnosis on survival statistics in carcinoma of the uterine cervix, *Amer. J. Obstet. Gynec.*, 97:739-749, Mar., 15, 1967.
89. Ruch, R. M., Blake, C., Abon, A., Lado, M., and Ruch, W. A.: The changing incidence of cervical carcinoma, *Amer. J. Obstet. Gynec.*, 89:727-731, July 15, 1964.
90. Schiffer, M. A., Greene, H. J., Pomerance, William, and Moltz, A.: Cervical conization for diagnosis and treatment of carcinoma in situ, *Amer. J. Obstet. Gynec.*, 93:889-895, Nov. 15, 1965.
91. Schiller, W., Daro, A. F., Gollin, H. A., and Primiano, N. P.: Small preclerative invasive carcinoma of the cervix, *Amer. J. Obstet. Gynec.*, 65:1088-1098, May, 1953.
92. Schulz, B., Carlson, D. J., and Birge, E. A.: Optimum spacing of repeat follow-up, *JAMA*, 168:248-250, Sept. 20, 1958.
93. Scott, R. B., and Reagan, J. W.: Diagnostic cervical biopsy technique for the study of early cancer, value of the cold knife conization procedure, *JAMA*, 160:343-347, Feb. 4, 1956.
94. Scott, R. B.: Clinical treatment of dysplasia and carcinoma in situ of the cervix: *From Dysplasia, Carcinoma in situ and Microinvasive Carcinoma of the Cervix Uteri*, compiled by Laman A. Gray, Charles C Thomas, Springfield, Ill., 1964, Chap. 14.
95. Siegler, E. E.: Microdiagnosis of carcinoma in situ of the uterine cervix, a comparative study of pathologists' diagnoses, *Cancer*, 9:463-469, May-June, 1956.
96. Siegler, Edward E.: Histomorphology of carcinoma in situ, *Acta Cytol.*, 5:275-278, 1961.
97. Silbar, E. L., and Woodruff, J. D.: Evaluation in biopsy in intraepithelial carcinoma of the cervix, *Obstet. Gynec.*, 27:89-97, Jan., 1966.
98. Stallworthy, John: Post-operative hemorrhage after conization of cervix; *From Int. Correspond. Soc. Obstet. Gynec.*, Series V: 202, Dec. 1, 1964.
99. Tarkington, C. N., and Tweeddale, D. N.: Avoidance of diagnostic pitfalls in vaginal cytology, *J. Kentucky Med. Ass.*, 64:578-579, July, 1966.
100. Thomison, J. B., and Tosh, R. H.: Evaluation of punch biopsy in the diagnosis of carcinoma in situ of the cervix uteri, *Amer. J. Obstet. Gynec.*, 84:98-100, July 1, 1962.
101. Ullery, J. C., Bouselis, J. G., and Botschner, A. C.: Microinvasive carcinoma of the cervix, *Obstet. Gynec.*, 26:886-875, Dec., 1965.
102. Vallasanta, U., and Durkan, J. P.: Indications and complications of cold conization of the cervix, *Obstet. Gynec.*, 27:723, May, 1966.
103. Wied, G. L., and Hohl, G. F.: Vaginal, cervical and endocervical cytologic smears on a single slide, *Obstet. Gynec.*, 14:362-367, Sept., 1959.
104. Wied, G. L.: An international agreement on histological terminology for lesions of the uterine cervix, *Acta Cytol.*, 6:235-236, May-June, 1962.
105. Younge, P. A.: Premalignant lesions of the cervix: Clinical management, *Clin. Obstet. Gynec.*, 5:1137-1147, Dec., 1962.
106. Younge, P. A.: The natural history of carcinoma in situ of the cervix uteri, *J. Obstet. Gynaec. Brit. Comm.*, 72:9-12, Feb., 1965.

The Incidence of "Silent" Coronary Heart Disease

GEORGE L. KEMP, M.D. AND
MYRVIN H. ELLESTAD, M.D., *Long Beach*

■ *In a group of clinically normal male executives subjected to maximal treadmill stress testing, the occurrence of ischemic ST segment responses was in all cases unaccompanied by pain, while in a clinically suspect group a large proportion of those having ischemic ST segment responses did not have chest pain.*

While a significant number of persons have no subjective sensation of pain while having ischemic ST segment changes on the electrocardiograph during or after maximal treadmill exercise, occasionally atypical pain may occur during or following exercise. Maximal treadmill stress testing is useful in discovering "silent" coronary artery disease.

THE INCIDENCE OF unsuspected coronary heart disease detected by exercise stress testing has been reported by various investigators^{3,8,10,13} as ranging from 0.5 percent to 29.7 percent, variations depending upon the method employed for exercise stress, the population studied and the criteria used. Lester and associates⁶ reported in a comparative study that there was a higher incidence of segmental ST depressions associated with maximal stress testing in an apparently normal group than was associated with sub-maximal stress testing. This finding is similar to the observations of Bellet and Muller² and Doan and associates.⁴

The present study was undertaken to compare the incidence of ischemic ST segment abnormality in a clinically unsuspected group and to determine, by age groups, the incidence of chest pain occurring with ST segment abnormality on maximal

treadmill stress testing. The value of such a study lies in the discovery of clinically unsuspected persons having coronary heart disease without any warning of impending complications.

Material and Method

Two hundred and eighty-four male executives who were referred for routine examinations were included in this study. The age range was from 31 to 70 years. None of the group admitted to having had chest pain or symptoms suggestive of angina pectoris. The results of physical examination, routine 12-lead electrocardiogram and chest x-ray films were normal in this group. One thousand patients in a second group referred for maximal treadmill stress testing were also studied to determine the incidence of ischemic ST segment changes without evidence of co-existing pain. Patients in this group were suspected on clinical grounds of having coronary insufficiency or had been referred by their physicians for baseline treadmill stress tests

From the Division of Clinical Physiology, Memorial Hospital of Long Beach.

Reprint requests to: Memorial Hospital of Long Beach, 2801 Atlantic Avenue, Long Beach 90801 (Dr. Ellestad).

S-T SEGMENT CHANGE WITH EXERCISE

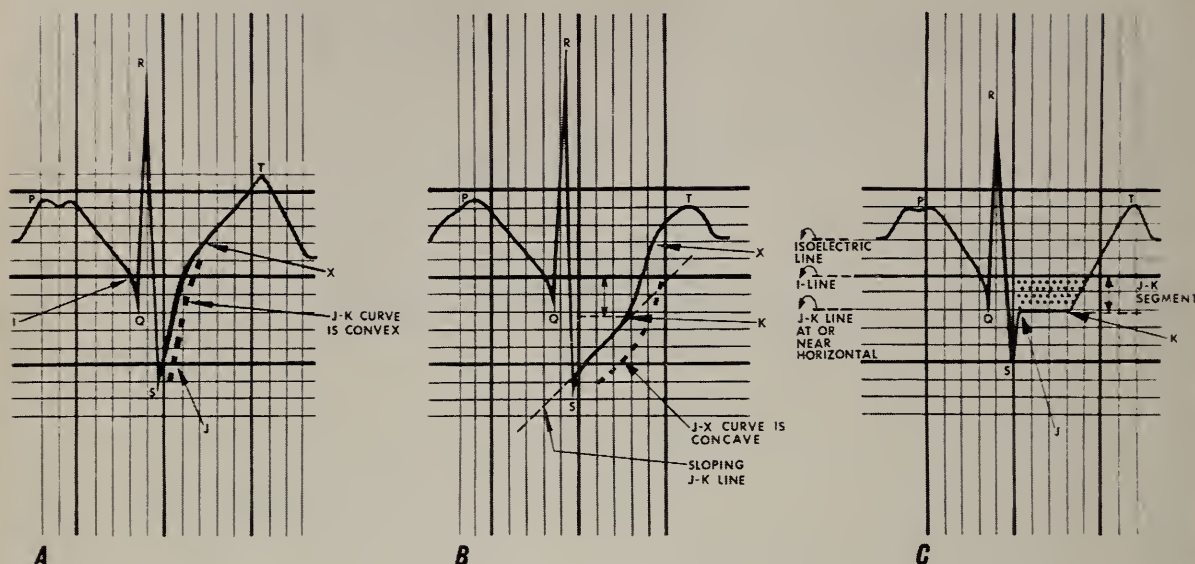


Figure 1.—A. This ECG complex demonstrates the normal J-point depression which occurs frequently following maximal exercise. B. The slow return of the ST segment to the baseline with a 2 mm or more depression of the K to isoelectric line interval is interpreted as an ischemic ECG response. Lesser degrees of depression of this interval with concavity of the J-X curve is interpreted as equivocal. C. There is depression and straightening of the ST segment of at least 2 mm for at least 0.08 seconds. This would meet our criteria for a clearly positive or ischemic ST segment response to treadmill exercise.

as part of a preoperative evaluation. There were 205 females and 795 males in this group with ages between 7 and 85 years. The patients, who were placed in the protocol in consecutive order of referral, represented a hospital laboratory population, as contrasted with the executive group who were not clinically suspected of having pathological changes. Patients receiving digitalis were instructed to discontinue this medication for two weeks before treadmill testing, since this medication is known to produce false-positive results.⁵ No attempt was made to categorize the 1,000 patients as to obesity, smoking habits or menopausal status, for we were interested only in the incidence of ischemic ST segment changes without co-existing pain.

The method used for maximal treadmill stress testing has been previously described.⁵ The baseline electrocardiogram (ECG) and the after-exercise ECG were recorded in the sitting position, while

supine ECG tracings were taken if suspicious but non-diagnostic ST depression was noted on the oscilloscopic monitor following exercise. Each patient was encouraged to complete the test; however, the exercise was terminated if the patient became exhausted, if a moderate reduction in blood pressure occurred, if multiple premature ventricular contractions or ventricular tachycardia appeared, or if progressive ST depression or progressive chest pain during exercise occurred. The patient's maximal pulse rate response to graded exercise was compared with the maximal predicted pulse rates compiled by Robinson.¹² In this way we could determine whether or not the patient had been maximally stressed, as there is a good correlation between maximal pulse rate and maximal cardiac output.^{1,7,11,14}

Ischemic ST segment changes on the electrocardiogram associated with maximal exercise stress is arbitrarily defined as a 2mm ST depression below

TABLE 1.—Data on Development of Pain in Subjects with "Ischemic" Response to Maximal Treadmill Stress Tests

Ages	Total	Men		Ages	Total	Women	
		With Pain	Without Pain			With Pain	Without Pain
31-40	15	2 (13%)	13 (87%)	31-40	3	2 (67%)	1 (33%)
41-50	74	30 (41%)	44 (59%)	41-50	16	7 (44%)	9 (56%)
51-60	74	23 (31%)	51 (69%)	51-60	12	5 (42%)	7 (58%)
61-70	29	11 (38%)	18 (62%)	61-70	12	8 (67%)	4 (33%)

the I-line persisting for at least 0.08 seconds (Figure 1). J-point depression is considered a normal finding with maximal stress. T-wave changes by themselves are not considered in the evaluation of ischemic response to exercise if there are no co-existing ST segment abnormalities.

Results

As they wished to have a satisfactory endurance report, the executives tested were motivated to perform at their maximal levels of endurance. All of the subjects performed maximal treadmill stress testing without complications and none of the subjects had to be stopped because of chest pain or electrocardiographic abnormalities as previously defined.

Of the 284 executives tested, there were 30 (11 percent) who, during or after exercise, had ischemic ST segment changes and ten (3.5 percent) who had equivocal ST segment changes. In no instance was chest pain present with ischemic ST segment abnormalities. In the 1000 subjects in the second group who were similarly tested by maximal treadmill stress, 192 of the 795 males (24 percent) and 43 of the 205 females (21 percent) had positive treadmill stress tests indicative of ischemic changes. When the incidence of chest pain associated with ischemic ST segment changes in the second group was studied in relationship to sex and age grouping (Table 1), it was apparent that in the majority of male subjects having ischemic ST segment changes, the changes occurred without a warning pain in the chest. In the female subjects, those in the 31-40 and 61-70 age groups had a higher incidence of chest pain associated with ischemic ST segment changes produced by maximal stress. Only 88 (37 percent) of the 235 patients with positive test results had chest pain. Sixty-three percent had ischemic changes without pain. The difference between these percentages was significant at less than the .01 level of probability. There was a slightly increased incidence of "painless" ischemic ST segment changes in the 41-50 and 51-60 age groups of women.

A comparison of males and females by age

group with the percentage of ischemic ST segment changes without pain disclosed a greater incidence of "painless" ischemic ST segment changes among men in the 31-40 age group (87 percent) than in women of that age (33 percent). This difference in percentage became negligible in the 41-50 year age group, with 59 percent of the men and 56 percent of the women having "painless" ischemic ST changes with stress testing. The trend was similar beyond the age of 41, although the men consistently had a greater incidence of positive treadmill stress tests without subjective evidence of pain.

Discussion

The use of a standardized treadmill maximal stress test was of value in the discovery of ischemic heart disease in 11 percent of a clinically unsuspected group of executives. It was of further interest that chest pain was not associated with the ischemic ST changes in any one of this group. Typical coronary pain in the absence of ST depression is extremely rare and we have not seen it more than two or three times. Despite the use of more stringent criteria for the establishment of ischemic ST segment abnormality than were used by Manning,⁸ Mattingly,¹⁰ or Brody,³ we were able to discover a significantly greater percentage of ischemic abnormalities with stress testing in a clinically normal group than those investigators did. It probably should be noted that the investigators mentioned did not employ maximal stress testing in their studies, but rather used the double Master test. Doan and his group⁴ found that they were able to demonstrate 1 percent positive ischemic responses out of 210 clinically normal men by the use of the double Master test, while ischemic ST changes were demonstrated in 9 percent of this same group with the use of maximal treadmill stress testing. Our findings tend to confirm Lester's⁶ and Doan's⁴ conclusions that maximal stress testing increases the diagnostic yield.

When consideration was directed to a large group of patients referred for exclusion of ischemic heart disease, it was found that out of 192 men with positive reaction to treadmill stress tests, there

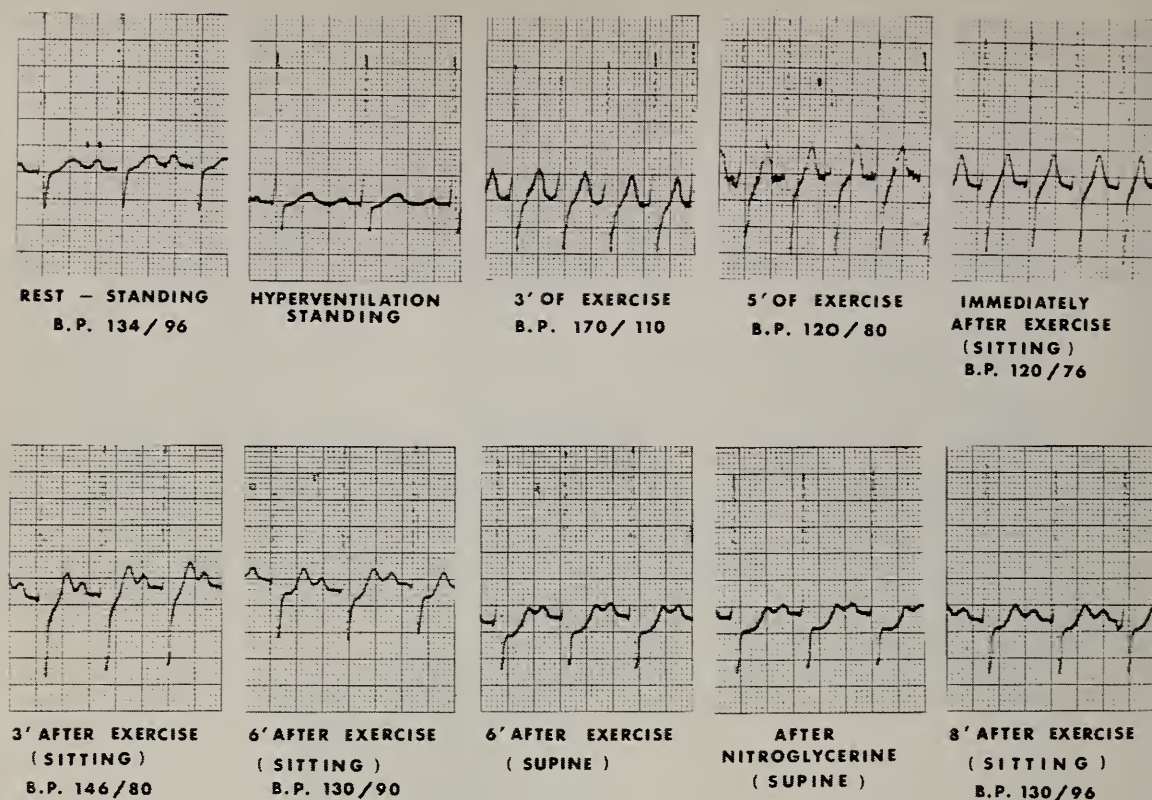


Figure 2.—A moderate rise in blood pressure was noted during the third minute of treadmill exercise at 1.7 mph. However, during the fifth minute of exercise at 3 mph the blood pressure fell to below the resting level. Ischemic ST changes did not appear until 6 minutes after exercise and further ST depression was observed while the subject was in the supine position. No significant change was noted after administration of nitroglycerine.

were 126 (66 percent) in whom the reaction occurred without chest pain. Of 43 women having positive treadmill stress test reaction, 22 had chest pain and 21 did not. In patients beyond the age of 40 there was a greater incidence of positive reaction to treadmill stress tests making a likely relationship between the subject's age and a positive response. Mason⁹ noted a similar relationship. When age groups were considered, it was demonstrated that the majority of men in all age groups having positive treadmill stress tests did not have associated pain. Women in the 31-40 year age group had a lesser incidence of positive treadmill stress tests without pain than did men, in the same age bracket. Beyond the age of 40, while the men had a greater percentage of positive stress tests without pain than did women, the relative incidence was strikingly similar, being highest in the 51-60 year age group.

As mentioned by Lester and coworkers⁶ there may be a difference in source populations to ac-

count for the different percentages of unsuspected coronary heart disease detected by exercise stress testing. Our discovery rate of 11 percent positive maximal treadmill stress tests in a clinically unsuspected group emphasizes the importance of screening various clinically normal populations in order to uncover silent coronary heart disease. Further, it is of importance to realize that the majority of men having treadmill stress test response indicating ischemia do not have concomitant chest pain. This is also true of middleaged women. This knowledge makes it imperative to instruct such patients to limit their physical activities to levels under that which produced ischemic ST segment changes on maximal stress testing, for they are not given a warning of their reduced coronary perfusion. It is a common practice to tell patients to use chest pain to signal the endpoint when exercising. This appears to be somewhat dangerous, for many patients may be stressing themselves to the point of early ventricular

failure, with dyspnea and fatigue as the only sensations recognizably related to the advanced ST depression.

Occasionally atypical chest pain during or after exercise will present a diagnostic challenge for evaluation. A 38-year-old man was able to perform treadmill exercise for 5 minutes before stopping due to dyspnea and fatigue. Chest pain did not develop during exercise, but he complained of aching in his left jaw and left arm 2 minutes after exercise. His ECG tracings (Figure 2) demonstrate no ischemic abnormalities until 6 minutes after exercise, at which time straightening and depression of the ST segments were noted. This ST segment depression was augmented by assuming a supine position which is a maneuver we have reported on earlier to enhance the yield of ischemic ST abnormality.⁵ This study was interpreted as positive for ischemic abnormality and 4 days later when the patient was being scheduled for coronary angiography, he suddenly dropped dead.

REFERENCES

1. Astrand, I., Astrand, P.-O., Christensen, E. H., and Hedman, R.: Circulatory and respiratory adaptation to severe muscular work, *Acta Physiol. Scand.*, 50:254, 1960.
2. Bellet, S., and Muller, O. F.: Electrocardiogram during exercise: Its value in the diagnosis of angina pectoris, *Circulation*, 32:477-487, Sept. 1965.
3. Brody, A. J.: Master two-step exercise test in clinically unselected patients, *JAMA*, 171:1195-1198, Oct. 1959.
4. Doan, A. E., Peterson, D. R., Blackmon, J. R., and Bruce, R. A.: Myocardial ischemia after maximal exercise in healthy men, *Am. Heart J.*, 69:11-21, Jan. 1965.
5. Kemp, G. L., and Ellestad, M. H.: The current application of maximal treadmill stress testing, *Calif. Med.*, 107:406-412, Nov. 1967.
6. Lester, F. M., Sheffield, L. T., and Reeves, T. J.: Electrocardiographic changes in clinically normal older men following near maximal and maximal exercise, *Circulation*, 36:5-14, July 1967.
7. Levine, H. J., Neill, W. A., Wagman, R. J., Krasnow, N., and Gorlin, R.: The effect of exercise on mean left ventricular ejection rate in man, *J. Clin. Invest.*, 41:1050, 1962.
8. Manning, G. W.: The electrocardiogram of the 2-step exercise stress test, *Am. Heart J.*, 54:823-836, Dec. 1957.
9. Mason, R. E., Likar, I. N., and Ross, R. S.: New system of multiple leads in exercise electrocardiography: Comparison with coronary arteriography, *Circulation* 30 (suppl. III), 3:123, 1964.
10. Mattingly, T. W.: The postexercise electrocardiogram, *Am. J. Card.*, 9:395-409, Mar. 1962.
11. Morehouse, L. E., and Miller, A. T.: *Physiology of Exercise*, The C. V. Mosby Co., 1948.
12. Robinson, S.: Experimental studies of physical fitness in relation to age, *Arbeitsphysiologic*, 10:251-323, 1938.
13. Rumball, C. A., and Acheson, E. C.: Latent coronary heart disease detected by electrocardiogram before and after exercise, *Brit. Med. J.*, 5328:423-428, 16 Feb. 1963.
14. Shock, N. W., Andres, R., Landowne, M., Norris, A. H., Simonson, E., and Swartz, F. C.: Aging of the cardiovascular system, *Nat. Conf. on Cardiovasc. Dis.*, 2:558, 1964.

A SCHEDULE OF ANTACIDS FOR ULCER PATIENTS

"Given an ulcer patient and given the problem of a practical therapeutic program, it seems to me that one can say, 'Okay, Mr. Smith, you take your breakfast at eight o'clock, your lunch at 12 o'clock noon, and your dinner at six o'clock. And now we know that food buffers and neutralizes for an hour or two hours, so you take your antacid at 9:30 or 10 o'clock, take another one at eleven, take other antacids at two and four o'clock in the afternoon, eight o'clock in the evening, and bedtime.' That's only six times a day, but together with the food, and then if you add an anticholinergic (preferably before meals because Chapman showed years ago that it's easier to get the effect of the anticholinergic before the stimulus of food than after), you can work out a practical program of dealing with peptic ulcer. I'm recommending this for the active ulcer patient. I do not wish to be in the position of saying this will really, absolutely prevent recurrences in 100 percent of cases, but it represents a practical approach."

—JOSEPH B. KIRSNER, M.D., Ph.D., Chicago
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The LSD Syndrome

— A Review —

HERBERT H. EVELOFF, M.D., *Los Angeles*

■ LSD (lysergic acid diethylamide) is a powerful bio-active substance related to serotonin in structure. Its actions generally affect autonomic, sensory and psychological functions. Autonomic stimulation is varied. Sensory responses are usually visual, involving heightened and distorted color perception and fusion of sensory impressions. Psychological responses include a feeling that a unique experience is occurring; feelings of depersonalization; pronounced fluctuation of mood; time and space distortions; autistic phenomena; fluctuation of aggressive drives (usually reduction); and spontaneous reoccurrence of the LSD experience.

The subjective responses can be related to three basic phenomena: (1) expectation; (2) loss of characteristic modes of perceptual and cognitive patterning; and (3) hypersuggestibility.

The major adverse reactions are: (1) chronic drug dependence including subsequent personality changes and depressive reactions; and (2) acute ego dissolution. These reactions usually occur in already emotionally ill people. Most of these users fall into two groups, those with unresolved identity problems and those with severe ego abnormality. The majority of adverse reactions are of the chronic drug dependence type and are usually seen in adolescents and young adults who have not negotiated the age-appropriate tasks of forming and integrating the various identities that are the composite of their life experiences.

LSD helps alleviate these stresses via some of its psychological properties as discussed. It also provides a nidus for the formation of a subculture where goals for social, sexual and vocational achievement are lower and idiosyncratic modes of adaptation are better tolerated. A smaller group of users who have serious reactions such as psychosis, rage reactions, homicidal and suicidal ideation are usually found to have preexisting ego abnormality such as ambulatory schizophrenia, chronic impulse disorders and borderline states. Although adverse reactions most often appear to be related to pre-morbid psychopathology, this is not invariably so. Further, there is as yet no reliable method to determine who will have an adverse reaction and what the nature of that reaction will be.

THIS ARTICLE WILL REVIEW THE LSD SYNDROME, including adverse psychological reactions. The types of people likely to use LSD and those likely to suffer untoward reactions are also discussed.

LSD (lysergic acid diethylamide) was synthesized in 1938 by Hoffman, a Swiss chemist. In 1943 he fortuitously discovered its psychedelic properties. It is a semi-synthetic amide of ergot which is effective in trace amounts. It is one of the most powerful bio-active substances known.

Its exact mode of action is yet to be discovered. It has been stated that the sensory and psychological responses noted with the drug are seen after most of it has cleared the brain, suggesting an indirect rather than a direct effect.⁸ LSD resembles serotonin in structure (indole nucleus) and is postulated to interfere with serotonin metabolism.⁴

Upon ingestion, the initial reaction is one of autonomic stimulation which usually has its onset in from 20 minutes to one hour. These are most commonly pupillary dilation, sweating, pilo-erection, tachycardia (occasionally bradycardia), respiratory stimulation or depression (mild) and occasionally slight nausea.

Sensory and psychological responses usually occur without alteration of consciousness except when massive doses are taken (a toxic delirium can then be seen). This is in contrast to other substances—such as lead, narcotics, alcohol—that share with LSD the ability to produce perceptual and emotional distortions but which alter consciousness.

Tolerance to LSD occurs but is easily lost and withdrawal symptoms are absent or mild.⁵ They consist of slight restlessness and irritability which may be psychological rather than physiological.

The acute responses to LSD are summarized below:^{7,9}

Sensory Responses

- *Distorted Color Perception.* Colors appear to be intensified and often seem to throb and undulate as if alive. Spontaneous bursts of kaleidoscopic color can occur without any external stimulation in some subjects. These sensations are accompanied by an overwhelming sense of fascination and wonderment that almost defies description.

- *Fusion of Sensory Impressions (synesthesia).* An auditory or tactile stimulus may stimulate a

color response or, less commonly, the reverse occurs.

Psychological Responses

- *A feeling that the subject is undergoing a unique experience.* There is a feeling of transcendence, of great insight, of something very revealing and meaningful occurring about the user and his relationship to the world. These revelations are often difficult to relate.

- There are a group of sensations which can be subsumed under the rubric of *depersonalization*. These feelings are variously described as being outside of one's body, of observing oneself, of being a disembodied spirit, of feeling strange. Occasionally there is a confusion of self with a sensory stimulus, "Am I hearing the music or is the music me?" Loss of body boundary is commonly seen, leading to claims of body fusion and mental telepathy.

- *There are pronounced fluctuations of mood* although the prevailing mood is usually one of pleasant reverie during the period that the drug is exerting its pharmacologic action (three to ten hours). Euphoria is not uncommon. The post drug phase is often marked by a feeling of despair.

- *Time and space distortions* are quite common. Five seconds may seem like hours and the converse may also be true. Objects may seem infinitesimally small or frighteningly huge. Two-dimensional figures can appear to have volume and depth.

- There is an *autistic withdrawal and preoccupation, even fascination, with one's own ongoing perceptions and thoughts*, although habitual users do not prefer to take LSD alone. However, at times, this preference has more to do with a need for a "sitter" or "tripmaster" to insure against a "bad trip" rather than a need for social interaction. Mental organization and control is often restored by the reassurance of such guides, although this is by no means always the case. On occasions, unfortunate reactions to LSD have resulted from the "tripmaster" reneging on the role entrusted to him.

- More often than not, there is a *reduction of all aggressive drives* even in subjects who have a long history of acting out violent impulses. Rage reactions do occur, but are seen less frequently.

- Often there is an unpredictable unheralded *return of the LSD experience* without consumption of the drug even if the last dose has been taken months before.

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Reprint requests to: UCLA Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles 90024.

- There has been a suggestion that brain damage and genetic abnormalities can occur from chronic use of LSD, but this has not been conclusively proved in man.

Three Basic Phenomena

Most of the subjective responses listed above are dependent upon or intimately related to three basic phenomena.

The Effect of Expectation

The first of these is the effect of expectation. The form and intensity of the LSD experience is in large part shaped by the mental attitude ("set") of the subject and the setting in which the drug is taken. Anything that can influence the set or setting can be instrumental in determining the subjective experience that is reported—for instance, previous knowledge of expected response; comments by friends; surroundings at time of ingestion (that is, home, psychiatrist's office, research laboratory, party). The effect of subject expectation is so profound that it alone may suppress the entire LSD experience itself, including sensory responses if the subject is decidedly skeptical or otherwise unwilling to release himself to the drug.

Loss of Cohesiveness

If the subject will allow the experience to proceed, the second basic phenomenon occurs, namely, the loss of characteristic modes of perceptual and cognitive patterning. This represents the acute response to the drug. The subject's usual apperception of sensation, space, time, thought and emotion changes dramatically. That which took a lifetime to jell into a characteristic *Weltanschauung* abruptly dissolves. Each element of the mind is released, free to float boundlessly in a three-dimensional phantasmagoria of jumbled fragments. It is as if central impulses leap across ordinarily resistant synapses and burst forth out of their accustomed channels, spilling into one another and down pathways not usually traversed. The elements of mental life freed from their moorings fuse in strange, fascinating and sometimes frightening combinations.

Hypersuggestibility

This loss of cohesiveness makes possible the third basic phenomenon—hypersuggestibility. With his reflexive modes of perception and cognition

jarred loose, the user's judgment of the stimuli impinging upon him is impaired. What someone else says or what the subject thinks, be it frightening or pleasurable, can seem to be a perceptual and emotional reality. This difficulty in ascertaining the significance of ongoing phenomena is not limited to stimuli from the environment or the suggestions of others but includes the subterranean thoughts and sensations emanating from the subject's own unconscious mind. Higher order (secondary process) thinking gives way to regressive (primary process) thinking. Reality testing can become faulty. Users have been known to jump off buildings after yielding to omnipotent infantile phantasies that they could fly, or to walk into the path of oncoming cars, having suggested to themselves the idea that they were invisible and without substance.

True hallucinations are uncommon. The subject is usually aware of the real nature of his perceptions but allows himself to subjectively misinterpret them much as occurs in hypnosis. However, in certain disturbed persons a failure to maintain this kind of control can lead to panic.

Major Adverse Reactions

The major adverse reactions to LSD ingestion are chronic drug dependence (including associated personality changes and depression), and acute ego dissolution (including psychotic states, panic reactions, rage reactions and suicidal ideation).^{2,3,6,10} In my experience, these adverse reactions occur principally (but not invariably) in already emotionally ill people. These can be broadly divided into two groups, those with unresolved identity problems and those with severe abnormality of the ego.

The majority of adverse reactions are of the first type mentioned, chronic drug dependence. These commonly occur in late adolescents and young adults who as a group have pronounced identity problems. While such identity problems are probably more prevalent in this generation (for reasons to be mentioned later) they are not peculiar to our times. Again, neither are the responses to these identity problems specific for this generation. There have always been troubled teen-agers who have turned to drugs but hardly any observer of the American teen life would deny that drug use is now considerably increased. It is worth while to examine the dynamics behind this dangerous escape toward drugs in general and LSD specifically.

At that point in life when the various fragments of the adolescent personality usually coalesce allowing the precipitation of well-defined social, sexual and vocational goals, these young people experience an overwhelming sense of diffusion and impotence. The prospect of leaving adolescence (whatever the chronological age) and making the commitments necessary for the attainment of mature intimacy, involvement and productivity threatens to leave unresolved dependency needs unmet.

Several considerations of our era accentuate these problems. Mass communication has made the teen-agers aware of the material rewards available to those who can master our technological age. But it also has presented them with an enormous challenge, one that not every adolescent can master. Also, it has made them aware of the moral hypocrisy of the adult world, further robbing them of a desire to embrace adult responsibilities.

The young person who feels completely unprepared to meet the demands of the culture handles this threat to his self-esteem by declaring a moratorium in the maturational process. He searches for a group¹ with a similarly arrested development where his own inadequacies will become just one unnoticed piece of the collective mosaic of psychopathology. Such groups, while appearing superficially independent, are actually utilizing mass reaction formation in the service of denying a wish for old symbiotic parental ties; ties, which in our affluent society, often take care of more dependency needs than are optimum for normal development. To foster this denial of their dependency needs, they adopt a *modus vivendi* as manifestly different from the parental model as possible. Legitimate protests against the materialism and loss of human values which characterize much of our society are used to obscure personal despair and justify personal failures. While protesting the hypocrisy of "the establishment," they engage in worshiping their own brand of rigid ersatz values—fusion substitutes for relationships, license for love, juxtaposition for involvement, and confused idealism for dedicated conviction.

Such youngsters are highly susceptible to the most common adverse reaction of LSD, namely, drug dependence. For the potential "acid head," defenses against warding off the despair of a vacuous existence do not work. The offer, within the group or out of it, of an easy solution to the unresolved problems of attaining individuation and

subsequent contact without fusion is readily accepted.

In some respects, the effect of taking LSD for the chronic user appears to resemble that obtained by other drugs. For instance, marijuana and methedrine, like LSD, can inject a euphoric diversion into a vacuous existence. However, LSD has some qualities which differ in kind or degree from other drugs. LSD has the ability to transform a wish into a concrete reality, allowing temporary gratifying "solutions" to all of the anxiety-provoking problems involved in attaining maturity. It has the ability to appear to provide instant "insight" into the complexities of life without a need to actually engage life. Also, unlike drugs such as heroin, the chronic use of LSD uniquely distorts the appraisal of the drug effect itself in that the heroin addict uncommonly obscures his awareness of a need to rely on a drug for emotional existence (if he does, withdrawal symptoms provide a painful reminder), while the chronic LSD user rationalizes and justifies his dependence on a drug as a way of life. All of these qualities set this drug apart from others and make it especially dangerous.

Aside from the satisfaction of dependency needs, the chronic user begins to get the acceptance he may not have otherwise obtained. He evaluates himself and his accomplishments uncritically and receives uncritical group endorsement for his activities, no matter how bizarre or worthless. Actually, whatever artistic, intellectual, musical, literary or other special ability he may have had, often undergoes degeneration rather than evolution.

Unfortunately, the disparity between the Disneyland of his LSD existence and the wasteland of his real life cannot be totally or eternally denied. Anxiety and depression must be continually ward off by an increased religious commitment to the group and its drug habits.

Those who took this detour from life because of a temporary impasse in the quest for ego synthesis, will eventually turn away from LSD. In my experience, this is actually the most frequent outcome for those who employ LSD.

Ego Disintegration

In addition to the adverse reaction of temporary or permanent LSD use and the already discussed related personal and social problems, this drug has been instrumental in precipitating ego disintegration such as psychotic reactions, rage reaction,

panic states, and suicide.¹⁰ The vast majority of psychotic and similar reactions have occurred in people who had preexisting disorders of ego deficit such as schizoid personality, borderline states and ambulatory schizophrenia. Eventually such people fail to tolerate the disorganizing effect LSD has on characteristic modes of perception and cognition, and their fragile defenses collapse.

While the person who seeks a fringe group has *a priori* some capacity as a social being for interrelating and some notion of coming to terms with existence, there are those whose profound need to fuse with an external source of sustenance is so great that even the substituted symbiotic ties of the group threaten their fragile egos. The only way to remain intact at all is to keep at a distance. Unfortunately, they therefore often do not enjoy the group support that tends to act prophylactically against psychosis. With their already tenuous grasp on reality further loosened by LSD, they become overwhelmed by unconscious terrorizing phantasies and frightening sensations of non-existence. Although many of these people are actually prepsychotic or latently psychotic, it cannot be said whether or not overt psychosis would have eventually occurred without use of the drug. That is, would some sick young people have made it through the turbulence of youth without a psychotic break had they not discovered LSD?

Of the attempted and successful suicides, some attempts have occurred to ward off or end the panic of ego dissolution, while others have come as a result of a sudden "insight" into a futile life, and some have occurred in the post-LSD period when the contrast between the "high" of their LSD experience and the "low" of their existence becomes too much to tolerate. A few suicide attempts have not been attempts at all, but accidental occurrences attributed to such beliefs on the user's part that he was invincible to pain or could stop cars with a glance.

Summarizing the conclusions concerning the adverse reactions (drug dependence, personality deterioration, psychoses, suicide) they are suffered most frequently, but not exclusively, by those who have a preexisting emotional illness. There are broadly two groups. The greatest number of users who suffer adverse reactions are those who fail to resolve various identity problems and thereby do not rise above adolescence, whatever their chronological age. LSD often eventually causes great anxiety and depression because of the disparity

between fulfilled wishes for achievement while "high" on the drug and the failure to achieve culturally expected goals while not taking it. They adopt a desperate *laissez faire* attitude toward themselves and others (which includes sexual activities). Unfortunately, group support and activities usually do little more than obscure their despair, rarely obviate it. As they drift farther away from the mainstream of life, their anxiety and depression fosters chronic drug use. Fortunately, the majority of those who try LSD eventually give it up.

A smaller group has more serious abnormality of ego. These people may disintegrate under the impact of the disorganizing effects of LSD, not only because of the seriousness of their already existing emotional disturbances but also because their pathologic state (for instance, schizoid traits or inadequate personality patterns) may secondarily prevent them from obtaining the group support that often sustains many other LSD users. Unfortunately, although there are some guidelines as to which type of LSD user is most likely to suffer a particular broad category of adverse reactions, there is certainly no reliable method of predicting who will or who will not have a deleterious reaction to the drug. The corollary is that no precaution guarantees even a psychiatrically normal person the safe use of this compound.

Conclusion

Most of the subjective manifestations of the LSD experiences can be related to three basic phenomena: (1) the role of pre-drug expectations; (2) a loss of characteristic modes of perception and cognition; (3) hypersuggestibility.

In the pre-drug phase, the subject's needs to experience (or not experience) any or all of the pleasurable or adverse reactions are related to those drug manifestations he will report. When he ingests the drug, its potentialities for acutely disengaging usual patterns of perception and cognition provide a variety of possible sensory and emotional experiences. In this fluid state, the subject is extremely sensitive to his own wishes and suggestions (conscious and unconscious) as well as to the suggestions of others. These suggestions can be transformed into emotional and perceptual realities. Although delusions and hallucinations do occur, the usual response is that the subject retains an awareness of the unreality of his experience.

Adverse reactions most commonly, but not invariably, occur in people who have a preexisting

emotional illness. These emotional illnesses can be divided in a larger group with identity problems and those with ego abnormalities. The role of LSD in the latter group who manifest serious adverse reactions is probably as a catalyst rather than a principal ingredient. However, the significance of LSD in this context should not be underestimated, since it has not been established whether or not such serious reactions would have occurred without such a "catalyst" present.

REFERENCES

1. Bowers, M. D., and Freedman, D. X.: "Psychedelic" experiences in acute psychoses, *AMA Arch. Gen. Psychiat.*, 15:240, 1966.
2. Cohen, S., and Ditman, K. S.: Prolonged adverse reactions to lysergic acid diethylamide, *AMA Arch. Gen. Psychiat.*, 8:475-480, 1963.
3. Fink, M., Simeon, J., Haque, W., and Itil, T.: Prolonged adverse reactions to LSD in psychotic subjects, *AMA Arch. Gen. Psychiat.*, 15:450-454, 1966.
4. Freedman, D. X.: Effects of LSD-25 on brain serotonin, *J. Pharmacol. Exp. Ther.*, 134:160, 1961.
5. Freedman, D. X., Aghajanian, G. K., Ornitz, E. M., and Rosner, B. S.: Patterns of tolerance to lysergic acid diethylamide, *Science*, 127:1173, 1958.
6. Frosch, W. A., Robbins, E. S., and Stern, M.: Unfavorable reactions of lysergic acid diethylamide (LSD) resulting in hospitalization, *New Eng. J. Med.*, 273:1235-1239, 1965.
7. Isbell, H., Bellerville, H. F., Wikler, A., and Logan, C. R.: Studies on lysergic acid diethylamide (LSD-25), *Arch. Neurol. Psychiat.*, 76:468-478, 1956.
8. Remmen, E., Cohen, S., Ditman, K., and Frantz, J.: *Psychochemotherapy: The Physician's Manual*, Western Medical Publications, 1962, Los Angeles, pp. 32-35.
9. Unger, Sanford: Mescaline, LSD, Psilocybin and Personality Change, A Review in *Perspectives in Psychopathology*, edited by James O. Palmer and Michael J. Goldstein, New York University Press, 1966, pp. 278-295.
10. Ungerleider, J. T., Fisher, D. D., and Fuller, M.: The dangers of LSD, *JAMA*, 197:389-392, 1966.

USING EPINEPHRINE WITH HALOTHANE ANESTHESIA

"Is it safe to administer epinephrine in the presence of halothane? Doctor [Ronald] Katz and his group in New York have come up with a formula in which they state that it is safe . . . to give locally injected epinephrine to the patient under halothane anesthesia provided, first, that adequate ventilation is assured. . . . If you are not properly ventilating the patient, you are building up carbon dioxide tension and producing endogenous catecholamine; the endogenous catecholamine will add itself to the exogenous catecholamine and you'll be in trouble. Second, one must administer the epinephrine in a solution of one in 100,000 to one in 200,000 only. More concentrated types of epinephrine are not indicated and can get one into trouble. Third, the dose in adults should not exceed 10 ml of one in 100,000 epinephrine in any given 10-minute period. . . .

"We feel that this is a potentially hazardous combination to use. It is difficult to be sure that the patient is being adequately ventilated, and it is difficult to be sure that the epinephrine is not being injected directly into the bloodstream, therefore causing a very high level in the circulating blood to the heart and a very intense stimulus to the heart."

—C. R. STEPHEN, M.D., Dallas, Texas
Audio-Digest Anesthesiology, Vol. 10, No. 17

Endoscopic Treatment of Hypopharyngeal Diverticula

IRVING L. WHITE, M.D., *Long Beach*

IT IS WELL RECOGNIZED that hypopharyngeal pulsion diverticula can be repaired by the external surgical approach. Endoscopic operation is the only other effective treatment. In spite of technical improvements with reduced complications in the one-stage diverticulectomy, with dissection and extirpation of the sac, it is still a long and radical operation. This is an important consideration in dealing with elderly, debilitated patients, as most of them are. Hence the speed and ease with which the endoscopic procedure can be accomplished makes it the treatment of choice for patients who are poor risks.

Pathogenesis of Diverticula

Development of hypopharyngeal diverticula (Figure 1) produces a bulge or herniation of mucosa through the weakened posterior midline of the inferior constrictor muscles above the cricopharyngeus muscle (stopcock).

An easily understood and visualized concept of the pathogenesis is that the bolus of food is pushed down the pharynx as the constrictor muscle is actively contracting in the normal process of deglutition. There is then failure of normal synchronous relaxation of the cricopharyngeus muscle in the cephalad end of the diverticular-esophageal party wall. This wall creates a plowshare effect, directing the food into the sac rather than into the esophagus. This sustained contraction, narrowing the normal lumen of the esophagus, tends to widen the opening of the developing diverticulum (Figure 1, B). Then as the diverticular pouch

enlarges and pulls downward, the resulting torsion pull on the esophagus has a kinking effect which causes a direct dropping flow of material into the diverticular sac as the narrowed esophageal lumen migrates forward and upward. Obviously, the more this process progresses, with enlargement of the sac, the more difficult it becomes for food to pass into the normal passages (Figure 2).

The sac is the product of the pathologic change, not the cause. On the contrary, the causative factor, the cricopharyngeal ring and the party wall divert the normal stream of food from the pharynx into the developing sac. Removal of the party wall, including the cricopharyngeus, would relieve both the cause of the pathologic state and the symptoms, without removing the sac.

Treatment

With the external surgical approach (diverticulectomy), the surgeon always must accept the risk of removing too much tissue (sac and esophageal wall), with the attendant complication of stricture, or incomplete removal and the possibility of recurrence. It has been observed that even when too little of the sac is removed and residual small sacculation is left, if the cricopharyngeus muscle had been resected at the time of delivery of the sac and its neck—that is, if the cricopharyngeus had been resected (Figure 3)—the patient would experience no symptoms despite postoperative dimpling or sacculation. As long as the cricopharyngeus is present and active, symptoms should be expected to recur (Figure 4).

In 1906 Mosher attempted to correct pulsion diverticula endoscopically by splitting the party wall with scissors. Mediastinitis developed in the

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Reprint requests to: 2865 Atlantic Avenue, Long Beach 90806.

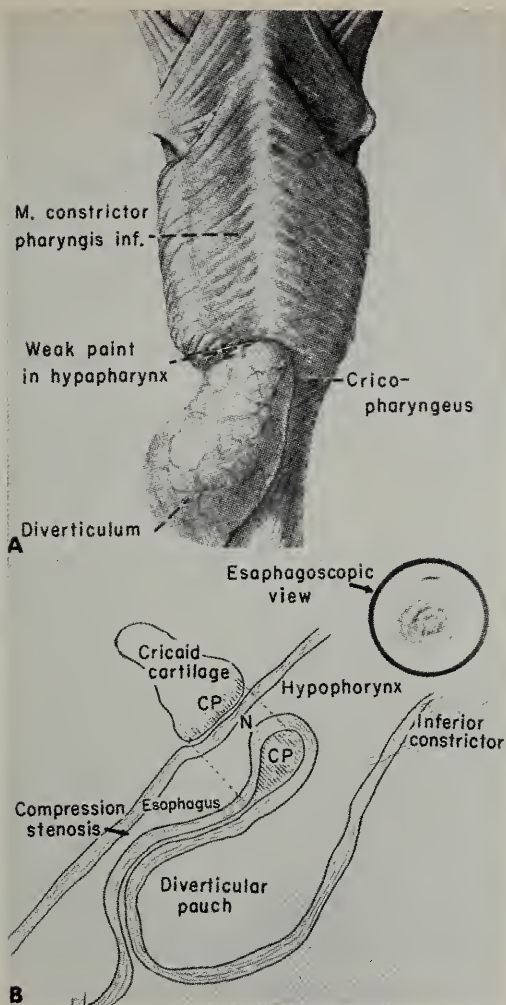


Figure 1.—A. Hypopharyngeal diverticulum is a mucosal bulging through weakened posterior midline of inferior constrictor muscle, above the cricopharyngeus. B. Diagram demonstrates how contraction of cricopharyngeus (C.P.) narrows normal lumen (N) while opening diverticular pouch. Insert shows narrowed lumen above the widened pouch orifice.

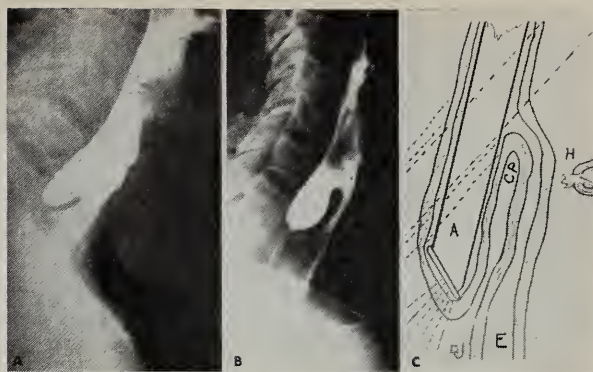


Figure 2.—Pathogenesis—As diverticulum enlarges, it pulls downward with a torsion pull kinking the esophagus, causing upward migration of the neck and narrowing the esophageal lumen (A to B). With enlargement of sac (C) there is a direct dropping flow into sac, material entering esophageal lumen only after sac is filled. (A. Esophagoscope passing directly into diverticular sac. E. Esophageal Lumen. C.P. Cricopharyngeus.)

second patient he operated upon in this way, and he made no further attempts.

Dohlman¹ in 1958 reviewed 100 cases in which he had used an operative technique that he had developed during the preceding 20 years. It is this technique, as further developed and described by Holinger,² that is being presented herein.

Technique in Endoscopic Repair

The armamentarium (Figure 5) consists of a double beaked esophagopharyngeal speculum which is used as a ground for the diathermy, a coagulating alligator forcep, an endoscopic diathermy knife and an endoscopic spatula guard. Endotracheal anesthesia is used.

With the beaks of the endoscope straddling the

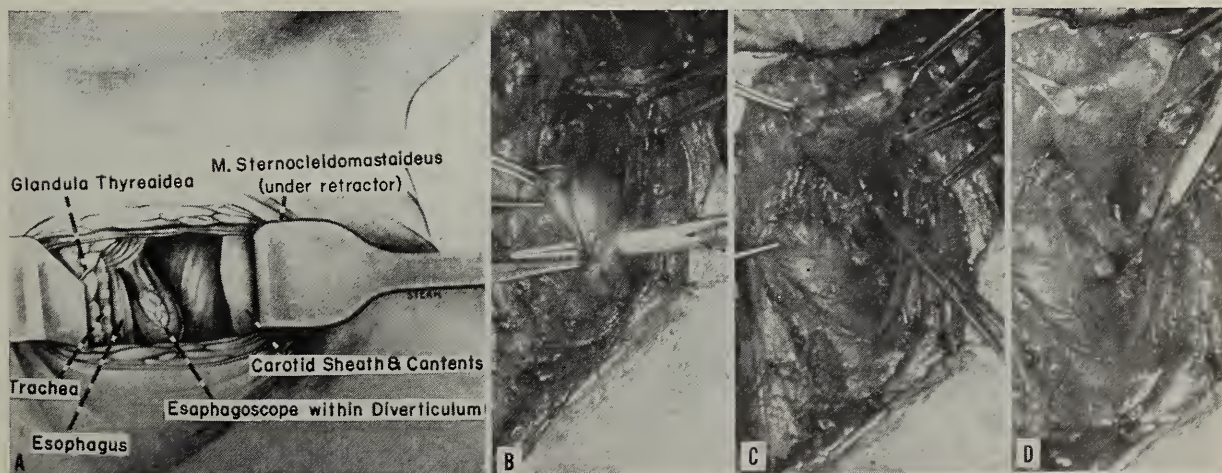


Figure 3.—External Diverticulectomy. A. Operative field sketch; B. Diverticulum delivered; C. Elevation of sac reveals neck of sac riding over cricopharyngeus muscle;

D. Cricopharyngeus muscle being sectioned with scissors. (Section of cricopharyngeus is key to successful cure of diverticulum whatever approach is used.)

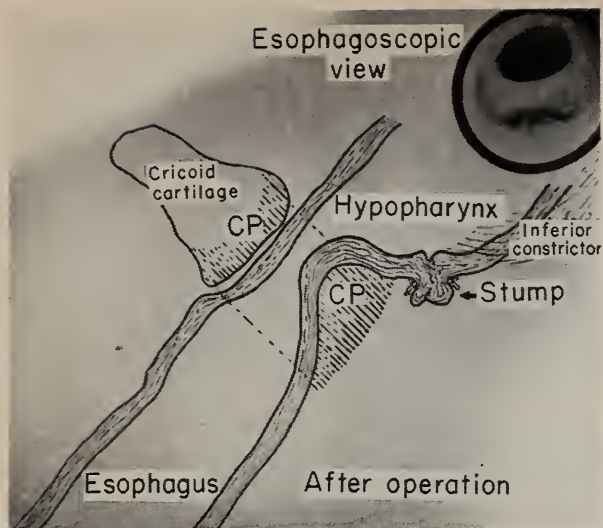


Figure 4.—Sketch demonstrates postoperative status excision of diverticulum with failure of removal of cricopharyngeus (C.P.) favoring recurrence of pathology.

party wall, one beak is inserted into the patulous sac orifice (Figure 6, A) and the other into the narrowed esophageal lumen. The diathermic coagulating alligator forceps is used to coagulate the midline of the party wall, after which the party wall is incised with the diathermy knife. The posterior wall of the sac is protected with the endoscopic spatula guard. Although the outline of the sac remains, the contents of the open walled sac empty into the esophagus, the retaining wall having been removed (Figure 6, B).

The procedure is accomplished in a few minutes.



Figure 6.—Technique A.—Dohleman endoscope in place with long beak of scope extending into esophagus and short beak into diverticulum. B. Specimen upper esophagus with diverticulum. Diverticular esophagus party wall has been split, with gaping opening of sac emptying into esophageal lumen (cadaver demonstration).

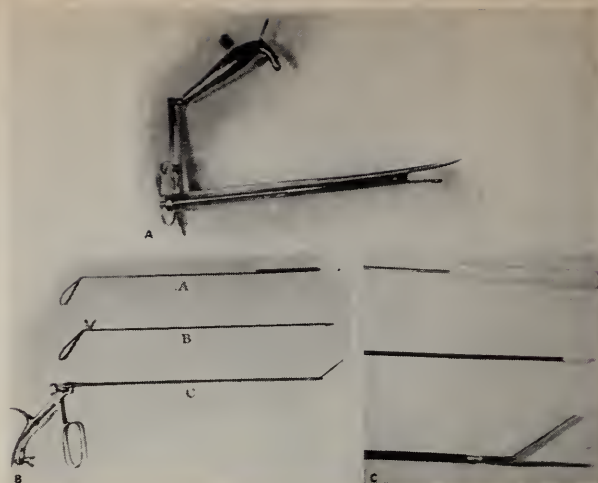


Figure 5.—Armamentarium consists of a double beaked esophagopharyngeal speculum (A), and diathermy instruments. A, endoscopic spatula guard; B, endoscopic diathermy knife; and C, coagulating alligator forceps.

Presentation Features

Cinefluoroesophagram

The author has successfully treated nine patients in the manner. Cinefluoroesophagrams were used to study hypopharyngeal diverticula and to document the diagnosis, the preoperative status and the postoperative results as described by Dohleman.¹ Following is a report of one representative case with selected frames of the cinefluoroesophagrams.

Report of a Case

The patient was a 66-year-old man with a history of increasing difficulty in swallowing, regurgitation, noisy gurgling on swallowing, recurrent aspiration of overflow of the pouch, and pneumonia.

Fluoroscopic esophagram examination revealed a massive hypopharyngeal diverticulum (Figure 7 A and B). Endoscopic treatment gave immediate relief of symptoms. A postoperative cinefluoroesophagram showed that, although the outline of the sac remained, the esophagodiverticular retaining wall with the cricopharyngeus had been incised, allowing the bolus contents to flow freely out of the sac and in a normal manner into the esophagus (Figure 7 C, D and E). The bulk of the bolus passed freely into the esophagus on swallowing, only an insignificant amount of material being retained after 5 minutes, and less still after 15 minutes (Figure 7 F and G).

Comment

Although Zenker's diverticula are occasionally

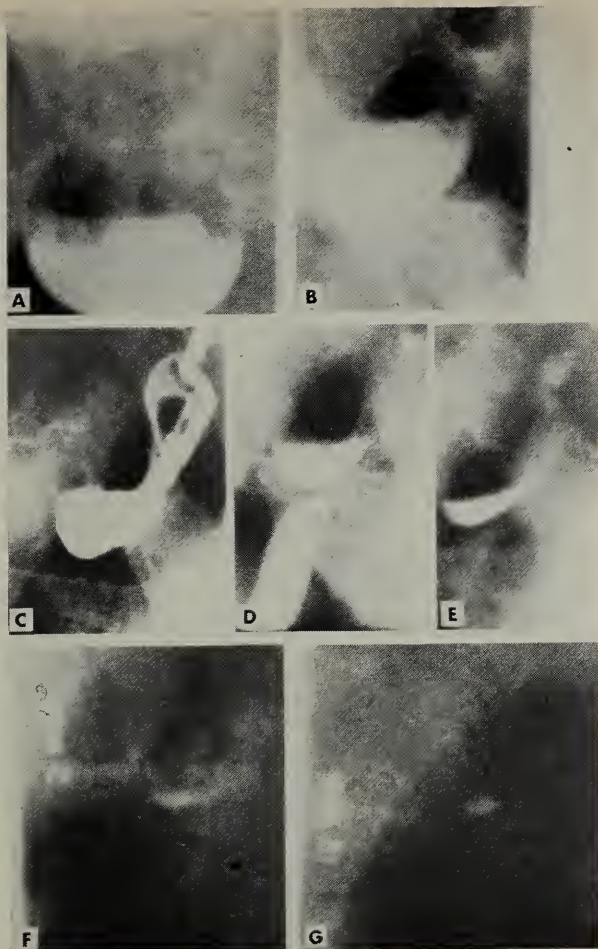


Figure 7.—Cinefluoroesophagram of reported case demonstrating: Figures 7-A, 7-B—AP and lateral views of hypopharyngeal pulsion diverticulum with massive retention, only overflow of the sac passes into esophagus. Figures 7-C, 7-D, 7-E—Appearance after resection of diverticular esophageal party wall, demonstrates unimpeded flow of bolus out of sac into esophagus. The insignificant residual is demonstrated in five and fifteen minute films. Figures 7-F, 7-G.

Photos all taken under identical enlarging distance factors of fluoroscopic tube, and development of illustrations; the variance in size of the lesion representing valid comparisons.

seen in patients in their fifth decade of life, almost all cases of pulsion diverticulum are in patients in their sixties or seventies. Age may be a factor in the development of the diverticulum; weakening of the inferior constrictor muscle as well as the dyskenesis between the contraction of the inferior constrictor and the failure of relaxation of the cricopharyngeus muscle may be part of the aging process. Inability to eat enough without distress may bring about hypoproteinemia. This, added to the debility and the often present pulmonocardiovascular infirmities consistent with their age, may make these patients serious anesthetic and surgical risks for any more than the simplest and shortest of procedures. The rapidity and ease by which endoscopic resection of diverticula is accomplished makes it ideal in such circumstances.

It is not intended, however, to replace the highly successful one-stage surgical procedure unless there are factors contraindicating this more extensive procedure. The incidence of recurrence of diverticulum after endoscopic repair has been reported as high as 7 percent, compared with at least 3 percent after the external approach.¹ Because of scar tissue and adhesions, reoperation externally for correction of recurrence after such a procedure is extremely hazardous, whereas reoperation after failure of the non-scarring endoscopic method can be easily accomplished. Moreover, the endoscopic procedure can be used without difficulty in cases of recurrence following either approach.

ACKNOWLEDGMENT: The author thanks Dohlman and Mattsson¹ and Holinger and Johnson² for permission to use many of the illustrations appearing in this article.

REFERENCES

1. Dohlman, G., and Mattsson, O.: The endoscopic operation for hypopharyngeal diverticula, *AMA Arch. Otolaryng.*, 71:744-752, May 1960.
2. Holinger, P. H., and Johnson, K. C.: Endoscopic surgery of Zenker's diverticula, *Ann. Otol. Rhino. Laryng.*, 70:117-1123, 1961.



CASE REPORTS

Protein-Losing Enteropathy in Infectious Mononucleosis

HOWARD F. CORBUS, M.D., *Fresno*

A PATIENT with typical infectious mononucleosis was observed to develop features indicative of protein-losing enteropathy. Both disorders were self-limited and recovery was prompt and complete. No similar case was found in a review of the literature.

Report of a Case

A 19-year-old white man was admitted to hospital in December 1966 because of fever, malaise, nasal congestion, non-productive cough and weakness which had begun abruptly ten days previously. Three days after the onset of these symptoms, diarrhea developed, characterized by four to six loose bowel movements daily, without blood, which continued until admission to hospital. The diarrhea was associated with a 20-pound increase in body weight and the appearance of massive edema of the lower extremities, together with mild dyspnea. The patient did not have urinary frequency, dysuria, hematuria or dark urine and he had had no abdominal discomfort, nausea, vomiting or jaundice.

The past medical history was not contributory.

At the time of admission the patient did not appear acutely ill. The blood pressure was 140/70 mm of mercury, the pulse rate 80 and respirations

16 per minute, and temperature 38°C (100.4°F). Pertinent physical findings included enlarged and slightly tender lymph nodes in both posterior cervical chains and in both axillae. The pharynx was red, but no exudate was seen. No cardiac abnormalities were noted and the lung fields were clear to auscultation and percussion. The abdomen was soft and no definite fluid wave was detected.

The liver and spleen were not palpably enlarged. There was massive edema of the lower extremities and scrotum and extending to the iliac crests.

An x-ray film of the chest showed small bilateral pleural effusions but was otherwise normal. Significant laboratory determinations (Table 1) included the characteristic features of infectious mononucleosis, low plasma albumin concentration and the absence of any evidence of renal disease.

The patient was placed at bed rest and became afebrile. The hospital course was one of rapid recovery. Diarrhea ceased spontaneously and the edema cleared within one week. The serum proteins returned to normal and the patient thereafter remained in good health.

Discussion

Although it was not possible to perform specific tests with labelled albumin or polyvinyl-pyrrolidone in this patient, the history of acute diarrhea with rapid appearance of massive edema, lowered plasma albumin concentration, and the absence of renal disease make it highly likely that this patient experienced a protein-losing enteropathy (PLE) in association with infectious mononucleosis. Since there was no evidence of a chronic gastrointestinal disorder, this case resembles those cases described with acute gastroenteritis and PLE.^{1,2} Although PLE has been associated with many disorders,^{3,4,5,6} it has not been described in association with infectious mononucleosis; and indeed gastrointestinal involvement (except hepatic) in infectious mononucleosis is quite unusual.

From the Department of Medicine, Fresno General Hospital, Fresno. Submitted 22 May 1968.

Reprint requests to: Department of Medicine, Fresno General Hospital, 445 South Cedar Avenue, Fresno 93702.

TABLE 1.—Clinical Data in Case of Infectious Mononucleosis with Protein-Losing Enteropathy

Date	WBC	Lymphs	Heterophile	Total Protein	Albumin	SGOT	SGPT	Bun	Creatinine
12/28/66	5,100	63%	1:224	68	24
12/31/66	15,000	76%
1/ 4/67	14,400	73%	1:1792	5 gm %	2.5 gm %	34	18	17 mg %	0.8 mg %
1/12/67	7,600	74%	1:896	6.7	4.6

Serial urinalysis was completely within normal limits, with specific gravities ranging 1.020-1.025. Hemoglobin was 15 to 16 gm per 100 ml; lupus erythematosus preparations negative; Na, K, CO₂, Cl, all within normal limits.

Of the several mechanisms that have been offered to explain the protein loss in PLE,⁴ two might apply to the patient in the present case. Passive diffusion of protein between mucosal cells in association with increased pressure secondary to lymphatic obstruction has been postulated as the mechanism in a number of disorders, including lymphatic telangiectasia and congestive heart failure.² Since enlargement of lymph nodes may occur in any region in infectious mononucleosis, lymphadenopathy in the mediastinum or mesentery of the bowel might produce a similar picture. A more likely explanation would appear to be exudation through inflamed mucosal surfaces similar to that which occurs in other types of acute gastrointestinal disorders, including regional enteritis, ulcerative colitis and acute non-specific gastroenteritis.⁴ In the present case the temporal relationship of edema and hypo-albuminemia to diarrhea suggests the latter mechanism (or conceivably a combination of the two mechanisms).

Pleural effusion has been reported in association with infectious mononucleosis, but the cases in the literature are unlike the present case. One of the

patients had a unilateral effusion,⁷ and in the other the effusions were associated with bilateral pulmonary infiltrations.⁸ Neither had peripheral edema. The pleural effusion in the present case was undoubtedly due to hypo-albuminemia.

Summary

A patient with infectious mononucleosis accompanied by a transient and self-limited protein-losing gastroenteropathy, a condition not previously associated with mononucleosis, is described.

REFERENCES

1. King, M. J., and Joske, R. A.: Acute enteritis with temporary intestinal malabsorption, *Brit. Med. J.*, 1324, 30 Apr. 1960.
2. Waldman, T. A., Steinfeld, J. L., Dutcher, T. F., Davidson, J. D., and Gordon, R. S.: The role of the gastrointestinal system in "idiopathic hypoproteinemia," *Gastroenterology*, 41:197, Sept., 1961.
3. Waldman, T. A.: Protein-losing enteropathy, *Gastroenterology*, 50:422, Mar. 1966.
4. Jeffries, G. H., Holman, H. R., and Sleisenger, M. H.: Plasma proteins and the gastrointestinal tract, *New Eng. J. Med.*, 266:652, 29 Mar. 1962.
5. Gordon, R. S., Waldman, T. A., and Laster, L.: Protein-losing enteropathy, *DM*, 3 Aug. 1966.
6. Jarnum, S.: Protein-losing gastroenteropathy, Blackwell Scientific Publication, Oxford, 1963.
7. Eaton, O. M., Little, P. F., and Silver, H. M.: Infectious mononucleosis with pleural effusion, *Arch. Int. Med.*, 115:87, Jan. 1965.
8. Vander, J. B.: Pleural effusion in infectious mononucleosis, *Ann. Int. Med.* 41:146, July 1954.

A WAY TO FIND THE SITE OF A BREAST PAPILLOMA

"If a patient has a bloody discharge from the nipple (and I don't believe that cytology is going to help much), take your finger and start at the top of the breast at 12 o'clock and stroke down to the nipple like the spokes of a wheel. Keep going around and find the place where you can push and express a little blood; if you can do this repeatedly, then explore that area and you're quite likely to find the exact location of a papilloma."

—A. H. LETTON, M.D., Atlanta, Georgia
Audio-Digest Surgery, Vol. 15, No. 17

The Clinician's Approach To Drug Interactions

HOWARD F. MORRELLI, M.D., AND KENNETH L. MELMON, M.D., *San Francisco*

■ *Drug interactions are important causes of both unexpected toxic and therapeutic effects. Adverse reactions due to drug interaction are proportional to the number of drugs given and the duration of administration. Although drug interactions may be beneficial, they are most often recognized when they increase mortality or morbidity. The frequency of adverse drug interactions in clinical practice makes it mandatory for physicians to know the drugs and mechanisms involved.*

A drug may potentiate or antagonize the effects of another drug by direct chemical or physical combination, by altering gastrointestinal absorption, by influencing metabolism, transport, or renal clearance, by changing the activity of a drug at its receptor site, or by modifying the patient's response to the drug by a variety of means.

This article stresses the importance of avoiding multiple drug therapy. When such treatment is unavoidable, patients must be carefully observed for evidence of intensified or diminished drug effect. Only this permits the detection and prevention of untoward drug interactions.

IN RECENT YEARS facts have become known that make the common but irrational practice of polypharmacy untenable. Conservative estimates of adverse drug reactions have soared despite the shortcomings of incomplete or biased sampling of patients due to: (1) lack of objective criteria of what actually comprises a reaction, (2) incomplete reporting by physicians and (3) the natural reluctance of physicians or paramedical personnel to attribute an adverse change in a patient's condition to the drugs selected for his treatment.¹ Despite

the many factors that lead to underestimation of reaction incidence, it has become unequivocally clear that a major determinant in the development of toxic effects is the number of drugs administered during any period to a patient.² Mistakes in administering drugs are encountered when more than a single compound is ordered.³ Adverse reactions are directly proportional to the number of drugs given and the duration of administration.⁴ Since the average in-patient receives six drugs daily,⁴ it is no wonder that reaction rates are high.

These reactions are of practical importance: they cause mortality, morbidity, increases in duration of hospital stay and requirements for extra medical attention, patient inconvenience and expense. Their additional importance extends to public health considerations. During a time of

From the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology and Cardiovascular Research Institute, University of California Medical Center, San Francisco.

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Reprint requests to: Division of Clinical Pharmacology, University of California Medical Center, San Francisco 94122 (Dr. Morrelli).

overtaxed medical facilities we cannot afford significant iatrogenic contributions to the burdens put upon them.⁵

Potent therapeutic agents cannot be withheld from a patient whose disease may be ameliorated by their use. Unfortunately, potent agents carry with them serious risks, as part of their primary pharmacologic action or as side effects. The rationale of drug choice and the need for multiple drugs must be firmly established on both clinical and pharmacological grounds. When polypharmacy cannot be avoided, an awareness of the frequency and recognition of early reactions is mandatory. Such reactions or interactions may be recognized as a frank adverse effect, or more frequently by the subtle loss or exaggeration of the clinical effect of one of the drugs being given.

This article reviews the known basic mechanisms involved in drug interactions and gives examples of clinical importance. These examples are not intended to be complete, but provide the basis of facts already known. Extension of these principles will provide a valuable means for the detection of additional interactions, and ultimately may be a means of detecting other problems, such as pharmacogenetic anomalies in drug metabolism.⁶

General Considerations

Drug interactions may be clinically helpful, (probenecid extends the half-life of penicillin⁷) or harmful, (phenylbutazone and indomethacin may cause bleeding in patients taking coumarin anticoagulants^{8,9}). They may increase (see above), or decrease the half-life of the involved drugs (phenobarbital decreases cortisol¹⁰). They may augment (insulin and sulfonylureas) or antagonize (thiazide diuretics and sulfonylureas¹¹) the desired pharmacologic effect.

The number of drugs involved in interactions is too great to permit memorizing them by trade names. Classification by pharmacologic group and mechanism of interaction is feasible. This approach helps in diagnosing an interaction, in predicting its effects and duration, and in selecting the most logical and effective therapy for the patient.

An interaction may be the result of: (1) a direct physical or chemical combination, (2) altered gastrointestinal absorption, competition for protein binding sites or receptors, (3) increased or decreased metabolism of drug by induction, activation, or inhibition of drug metabolizing mi-

croosomal enzymes, (4) alteration of acid-base equilibrium and thereby drug distribution and renal clearance, and (5) alteration of hemodynamics or renal function that influence rates of renal excretion. Examples in each of these categories will be cited and the pharmacologic groups of drugs particularly likely to be associated with drug interactions will be reviewed.

Direct Chemical or Physical Interactions

Direct interactions usually depend on formation of low-energy chemical bonds (hydrogen, ionic and non-covalent). Sometimes the interaction may be useful: The anticoagulant effect of heparin is reversed by binding to protamine. Chelating agents such as ethylenediaminetetracetate have application in selected cases of hypercalcemia or lead poisoning. Chemical interactions may diminish the desired pharmacologic effects of drugs: Tetracyclines are chelating agents, and gastrointestinal absorption of these antibiotics is inhibited when given simultaneously with antacids containing multivalent cations (for example, Ca^{++} , Mg^{++} , or Al^{+++}).¹² Cholestyramine, a drug useful for pruritus in biliary cirrhosis by virtue of its ability to bind bile salts in the gastrointestinal tract, may also bind a variety of drugs within the gastrointestinal lumen, preventing their absorption.¹³ Kaolin-containing compounds have been shown to limit the gastrointestinal absorption of the antibiotic lincomycin.¹⁴ Heptobarbital reduces the intestinal absorption of bishydroxycoumarin.¹⁵ Many drugs are incompatible chemically or physically and cannot be used together in intravenous solutions. A recent report lists 104 such drugs, some of which are incompatible with 20 other drugs or vehicles.¹⁶ A handbook of chemistry or a knowledgeable pharmacist should be consulted before therapy with such drugs is begun.

Interactions During Intestinal Absorption

Many factors influence drug absorption from the intestinal tract. Primary phenolic amino acids compete for the same sites for transport. Drugs like alpha-methyl-dopa (an amino acid) might be absorbed slowly when other natural amino acids are ingested in foodstuffs. The state of ionization (determined by the pK), the molecular weight and the polarity of a drug are also factors in absorption. Many drugs are weak acids or weak bases and the proportion of ionized drug is dependent on the pH of its milieu. Un-ionized compounds

TABLE 1.—Interactions in Transport

Many drugs are reversibly bound to plasma and tissue proteins, particularly acidic drugs. Only free drug exerts pharmacologic effect. If a very highly bound drug like B is given with a moderately bound drug like A, the bound form of the latter is displaced, enhancing A's effects. See text for qualifications.			
	Percent Binding Drug A		Percent Binding Drug B
Plasma	1 Free	0.1 Free	
	9 Bound	0.9 Bound	
Cells	1 Free	0.1 Free	
	89 Bound	98.9 Bound	
<i>Drugs like A</i>		<i>Drugs like B</i>	
Pamaquine		Mepacrine	
Tolbutamide		Sulphafenazole	
Warfarin		Phenylbutazone	
Warfarin		Oxyphenbutazone, Sulfapyrazone	
Bilirubin		Salicylates, Sulfonamides	
Methotrexate		Salicylates, Sulfonamides	
Quinine		Pyrimethamine	
Sulfaethylthiadiazole		Phenylbutazone	

generally are more soluble in lipid than when they are ionized. In an un-ionized form they readily cross cell membranes. Ionized drugs are generally polar, or water-soluble, and transfer across cell membranes will be relatively slow. For this reason, weak bases are generally more rapidly absorbed than weak acids. However, absorption of weak acids in the small bowel is achieved because of the large surface area.¹⁷ Some drugs, such as iron, are absorbed best when the gastric content is highly acid; other drugs, such as penicillin G, are destroyed at low pH. The package insert of unfamiliar drugs should be consulted as a guide to their administration to ensure optimal absorption.

Interactions at Plasma or Blood Transport Sites

Many drugs are reversibly bound to plasma or tissue proteins (Table 1) and, when bound, they are pharmacologically inert. Displacement of a drug from its binding protein permits it to act, but also facilitates its metabolism or excretion. The net effect of such drug interactions depends on the rate of administration of the second drug, the magnitude and stability of the dose of the first drug, and the relative binding constants of each compound. In practice, chemically induced alterations in the amount of drug bound by protein account for many important toxic reactions. Sulfonylureas such as tolbutamide are bound avidly to protein.¹⁸ When sulfonamides are given in addition to sulfonylureas, the latter will be displaced and hypoglycemia may ensue. Studies have shown a pronounced delay in the plasma disappearance rate

of tolbutamide after sulfaphenazole was administered. Diminished hepatic metabolism or renal clearance could be responsible for the prolonged tolbutamide effect, but it is possible that the tolbutamide is displaced from a plasma protein to a tissue protein that releases it more slowly. By such means tolbutamide's disappearance from the body would be delayed. Likewise, phenylbutazone can displace warfarin from its binding protein and induce bleeding. Methotrexate, useful in leukemias, and sometimes used for severe psoriasis, may be displaced by highly acidic, protein-bound drugs such as salicylates and sulfonamides, causing pancytopenia.¹⁹

An interaction of similar type appears critical in antimalarial therapy. Quinacrine is very highly protein bound. If pamaquine is given simultaneously or shortly after quinacrine therapy, binding sites which biologically will inactivate the pamaquine are not available, and pamaquine toxicity (gastrointestinal, hematopoietic) will be seen.²⁰ Quinine is not bound as strongly to proteins as pyrimethamine, and when it is given simultaneously in conventional doses severe quinine toxicity (cinchonism, neutropenia) is produced.²¹

Release of endogenous substances from protein-binding sites can occur when acidic compounds are administered. Bilirubin, which is ordinarily bound to plasma proteins,²² may be released from binding protein and contribute to kernicterus if salicylates and sulfonamides are given during the neonatal period.²³

Many reports cite alterations in metabolism of one drug by another as the mechanism for prolonged or enhanced drug effect. Unless such reports are documented by appropriate pharmacokinetic studies, interactions in transport cannot be excluded as an underlying or contributing factor.

Interactions at the Receptor Site

Drug effects are determined in part by binding to areas on tissues or cells (receptor sites) (Table 2). The amount of drug which will reach a receptor may be predicted by its affinity constant (the ratio of association to dissociation constants of the receptor and the drug). Knowing that an affinity constant is great does not aid in predicting whether the drug will have primary or direct influence on the tissue (Table 2, Drug B). For example, atropine has a high affinity constant for acetylcholine receptors but possesses no pharmacologic action of its own. Its pharmacologic effect

TABLE 2.—Interactions at the Receptor Site

Some drugs, like A in the chart below, combine with receptors to form a complex that elicits a response. The concentration of A, and its affinity (k) for the receptor are determinants of the response. Other drugs, like B, have affinity (K) for the receptor, but the complex elicits no response. If the concentration of B or its affinity constant (K) is higher than A's, no response will be detected. See text for description of interactions.

Drug A + k Receptor →	Drug A-Receptor Complex →	Response
Drug B + K Receptor →	Drug B-Receptor Complex →	No Response
<i>Receptor</i>	<i>Drugs like A</i>	<i>Drugs like B</i>
Vessel alpha receptor	Norepinephrine	Phentolamine
Bessel beta receptor	Isoproterenol	Propanolol
Cardiac sino-atrial node	Acetylcholine	Atropine
Neuro-muscular junction	Acetylcholine	d-Tubocurarine
Neuro-muscular junction	Succinylcholine	Gallamine
Adrenergic neuron	Norepinephrine	Metaraminol
Adrenergic neuron	Norepinephrine	Guanethidine

depends on its high affinity constant which predicts that it will competitively block receptor binding of acetylcholine which ordinarily elicits a tissue response. Although acetylcholine has intrinsic activity with the receptor, it has a lower affinity constant than atropine, which blocks its tissue effects. This effect can be reversed by adding agents which will allow acetylcholine to accumulate and compete for receptor sites (for example, cholinesterase inhibitors like neostigmine or edrophonium) or by infusing acetylcholine.

Some drugs are distributed to specific tissues and have highly selective effects: D-tubocurarine and gallamine interfere with access of acetylcholine to motor end plates. Anti-sympathetic agents may also work by similar mechanisms: Alpha-stimulating agents like norepinephrine are competitively antagonized by phentolamine or phenoxybenzamine. Beta stimulation by isoproterenol is specifically and competitively antagonized by appropriate doses of propranolol. The adrenergic neurone and its granules can be considered receptors for the storage of norepinephrine—that is, norepinephrine has high affinity but negligible intrinsic activity at this site. An example of interaction which can lead to complex pharmacologic effects is provided by this drug receptor complex. Amphetamines or imiprimines (antidepressants) have been given during antihypertensive therapy with guanethidine. Guanethidine must be taken up by adrenergic neurones before it (1) depletes granular

stores of norepinephrine, and (2) prevents physiologic neuronal release of the diminished norepinephrine stores.²⁴ Amphetamines and imiprimines discharge both guanethidine and norepinephrine from the neurons, resulting in either hypertension (if large amounts of catecholamines are released) or loss of the antihypertensive effect of the guanethidine, if it is no longer allowed access to the receptor.²⁵

Knowledge of the mechanism of action of such drugs and their interaction by means of competitive effects on the receptor are the key to proper drug administration and understanding of adverse effects. Understanding interactions at specific receptor sites also leads to the proper choice of effective countermeasures. For example, hypertension which occurs in the example above, or after administration of large doses of guanethidine, could be effectively reversed by alpha blocking agents.

Some interactions require astute and constant observation for their detection. D-tubocurarine and gallamine act by polarizing the motor end plate, and are potentiated by certain antibiotics with similar activity (neomycin, streptomycin, polymyxin²⁶) and by drugs that cause potassium depletion, such as the thiazide diuretics.²⁷ Although the effects of d-tubocurarine and gallamine (polarizing muscle relaxants) can be reversed by cholinesterase inhibitors, this therapy is contraindicated during decamethonium (depolarizing) paralysis (Table 2).

Interactions by Accelerated Metabolism

Many compounds are metabolized by microsomal enzymes located predominantly in the liver. Enzymatic action usually results in pharmacologic inactivation of the drug but some drugs (dibenzylamine, for example) require metabolic activation. Many drugs induce hepatic microsomal activity nonspecifically and thereby increase metabolism of themselves or other agents²⁸ (Table 3). Phenobarbital and antihistamines are frequently administered in clinical practice and often thought of as relatively innocuous agents. Barbiturates are potent microsomal enzyme inducers and can accelerate the metabolism of antihistamine, cortisone, diphenylhydantoin and other drugs (Table 3). There is definite evidence that bishydroxycoumarin is more rapidly metabolized when given with phenobarbital. As a result, larger than usual amounts of the anticoagulant are required for a therapeutic

TABLE 3.—*Interactions by Altered Hepatic Metabolism of Drugs*

Certain drugs are able to influence the hepatic enzymes that metabolize drugs to inactive products. Those listed below are examples of known or potential clinical importance.		
Drugs that are reported to inhibit metabolism of other drugs:		
Chloramphenicol: Hexobarbital		
para-Aminosalicylic acid: Hexobarbital		
Oxyphenylbutazone: Bishydroxycoumarin		
Methandrosteneolone: Oxyphenylbutazone		
Monamine oxidase inhibitors: Perhaps many		
Drugs that induce their own metabolism:		
Barbiturates	Phenylbutazone	
Glutethimide	Tolbutamide	
Meprobamate	Probenecid	
Antihistamines	Diphenylhydantoin	
Drugs that enhance metabolism of other drugs:		
Phenobarbital:	Hexobarbital	Testosterone
	Phenylbutazone	Estradiol-17 β
	Diphenylhydantoin	Progesterone
	Griseofulvin	Cortisol
	Bishydroxycoumarin	Androstenedione
Antihistamines:	Pentobarbital	Androstenedione
	Testosterone	Progesterone
Diphenylhydantoin:		
	Cortisol	

increase in "prothrombin time." If the sedative drug is discontinued, as may happen when a patient is discharged from a hospital, the dose of anticoagulant required to maintain the prothrombin time in the therapeutic range will diminish. Appropriate action must be taken or bleeding will ensue. Many drugs show similar potential.^{28,29,30,31,32,33,34} Recognition of other examples of interactions related to altered metabolism will ultimately depend on clinical observations that lead to pharmacokinetic studies which will determine precisely the mechanisms involved in changes in rates of disappearance of a drug.

Interactions by Inhibited Metabolism

A number of drug interactions are based on inhibition of metabolism of one drug by the effects of another. Such effects may be produced by irreversible inhibition of an enzyme responsible for metabolism of the first drug or by competing as a substrate for the same enzyme. The xanthine oxidase inhibitor, allopurinol, prolongs the half-life and increases the effects of 6-mercaptopurine by inhibiting the enzyme responsible for the latter's metabolism.³⁵ The cancer chemotherapeutic agent must be given in less than usual doses to prevent serious toxicity.³⁶ Other possible examples of the same phenomena include potentiation of the hypoglycemic effects of tolbutamide and the toxic ef-

fects of diphenylhydantoin by Dicumarol®.^{37,38} In turn, tolbutamide extends the half-life of a similar chemical, sulfonamide. Such potentiation probably is produced by competition of the drugs for metabolizing enzymes. Potentiation occurs when sufficient amounts of drug are given to produce saturation of the affected enzymes.

Some drugs have complex mechanisms for potentiation of a second compound. Although it is true that monamine oxidase inhibitors (MAOI for example, pargyline and tranylcypromine) may potentiate the effects of tyramine by prolonging its half-life, inhibition of the oxidation of tyramine accounts for only part of the MAOI potentiation of tyramine's effect. During MAO inhibition, tissue stores of catecholamines increase. A significant contribution to the potentiated effect of tyramine and other catecholamine-releasing agents is the expanded catecholamine pool available for pharmacologic release, in addition to actual prolongation of the catechol releasing agent's half-life.³⁹

Altered metabolism may be solely responsible for potentiation of the action of sedatives, narcotics, anesthetics, antiparkinsons, antihypertensive agents, tricyclic antidepressants, insulin and oral hypoglycemic agents by MAOI, but care is required to assess the potential contribution of alteration in protein binding, renal clearance, or tissue responsiveness when one drug potentiates another.⁴⁰ Likewise, potentiation of similar classes of drugs by hydrazine derivatives such as isoniazid and the antineoplastic agent procarbazine, may be related to their MAOI.

Influence of Acid-Base Balance on Drug Action

One determinant of the concentration of a drug at its receptor site is related to pH, which affects drug distribution. The diffusion of lipid-soluble weak acids and bases depends upon their state of ionization. Ionized drugs diffuse poorly across cell membranes. Intracellular sites are normally more acidic than plasma; hence weak bases attain higher intracellular concentrations than weak acids. During pathologic processes, or as a result of therapeutic interventions, plasma pH may be altered, with consequent changes in the concentration of drugs at receptor sites. For example, plasma phenobarbital (site of action intracellular) falls with respiratory acidosis and coma deepens as the drug enters cells; the reverse obtains with ventilation or bicarbonate therapy.⁴¹ Mecamylamine is a weak base with an extracellular site of action;

SUMMARY OF SUBJECTS AND POTENTIAL CLINICAL CONSEQUENCES OF DRUG INTERACTIONS			SUMMARY OF SUBJECTS AND POTENTIAL CLINICAL CONSEQUENCES OF DRUG INTERACTIONS		
When the Patient Takes this Drug	And the Doctor Is Added	These Symptoms or Findings Might Result	When the Patient Takes this Drug	And the Doctor Is Added	These Symptoms or Findings Might Result
ANALGESICS			ANTIHYPERTENSIVES		
Aspirin	Anticoagulant Para-aminosalicylic acid Probenecid	Bleeding Salicylism Decreased uricosuric effect of Probenecid	Guanethidine	Amphetamine Anesthetic Levarterenol Mephentermine Metaraminol Phenothiazine Tricyclic antidepressant	Hypertension Hypotension Increased response Decreased response Decreased response Hypotension Hypertension or loss of antihypertensive effect
Meperidine	MAO inhibitor Phenothiazine	Enhanced sedation, possible cardiovascular changes Enhanced sedation, respiratory depression	Mecamylamine	Sympathomimetic Thiazide diuretic	Sympathomimetic sensitivity Increased antihypertensive effect
Phenylbutazone	Coumarin anticoagulant Sulfonylurea (oral hypoglycemic)	Chronic: Decreased anticoagulant effect Hypoglycemia	Methyldopa	Anesthetic Levarterenol MAO inhibitor Sympathomimetic	Hypotension Increased response to Levarterenol Hypertension Direct acting: Increased sensitivity Norepinephrine liberators: decreased effect
Phenylramidol (Muscle relaxant)	Bishydroxycoumarin Diphenylhydantoin	Bleeding Diphenylhydantoin toxicity (cerebellar signs)	Reserpine	Anesthetic Digitalis Anesthetic Levarterenol MAO inhibitor Metaraminol Phenothiazine a sympathomimetic (direct acting)	Increased anesthetic effect Bradycardia Hypotension Increased Levarterenol effect Excitation, blood pressure increase Pressor response (Decreased) Hypotension Increased response
ANTIBIOTICS			ANTINEOPLASTIC AGENTS		
Chloramphenicol	Penicillin Barbiturate Codeine	Decreased penicillin effect Enhanced barbiturate effect Enhanced codeine effect	6-mercaptopurine	Allopurinol	Pancytopenia
Griseofulvin	Anticoagulant Phenobarbital	Decreased anticoagulant effect Decreased griseofulvin effect	Methotrexate	Aspirin Sulfonamide	Pancytopenia Pancytopenia
Penicillin G	Chloramphenicol Tetracycline	Decreased penicillin effect Decreased penicillin effect	Procarbazine	(See MAO inhibitor)	(See MAO inhibitor)
Neomycin, Kanamycin, Streptomycin	Curare	Increased curare effect	BARBITURATES		
Lincomycin	Kaolin	Diminished lincomycin effect	Phenobarbital	Alcohol Anticoagulant Antihistamine	Increased alcohol effect Decreased anticoagulant effect Decreased antihistamine effect Additive sedative effect
Para-aminosalicylic acid	Barbiturate	Enhanced barbiturate effect	Phenylbutazone	Phenylbutazone	Decreased phenylbutazone effect
Sulfonamide	Anticoagulant Sulfonylurea	Increased anticoagulant effect Hypoglycemia	Diphenylhydantoin	Diphenylhydantoin	Decreased Dilantin effect
Tetracycline	Antacid with divalent cations Methicillin Chloramphenicol	Diminished tetracycline effect Incompatible in I.V. solution Incompatible in I.V. solution	Griseofulvin	Griseofulvin	Decreased griseofulvin effect
ANTIMALARIALS			MAO inhibitor	MAO inhibitor	Increased phenobarbital effect
Mepacrine	Pamaquine	Pamaquine toxicity, methemoglobinemia, neutropenia	Benzodiazepines	Benzodiazepines	Enhanced sedation
Pyrimethamine	Quinine	Quinine toxicity, cinchonism, neutropenia	Phenothiazine	Phenothiazine	Enhanced sedation
COUMARIN ANTICOAGULANTS			Steroid (Cortisol, androgen, estradiol 17 β , progesterone)	Steroid (Cortisol, androgen, estradiol 17 β , progesterone)	Decreased steroid effect
(e.g. Bishydroxycoumarin, Warfarin, etc.)	Antihyperlipemic agents Glutethimide Chloral hydrate Chlordiazepoxide Diazepam Griseofulvin Meprobamate Norethandrolone Oxyphenbutazone Phenobarbital Phenylbutazone Phenylbutazone Propylthiouracil Phenylramidol Quinidine Salicylate Sulfonamide Long acting sulfonamides Tolbutamide	Increased anticoagulant effect Decreased anticoagulant effect Decreased anticoagulant effect Decreased anticoagulant effect Decreased anticoagulant effect Anticoagulant resistance Increased anticoagulant sensitivity Increased anticoagulant sensitivity Decreased anticoagulant effect Increased anticoagulant sensitivity: Acute Decreased anticoagulant sensitivity: Chronic Increased anticoagulant effect Increased anticoagulant sensitivity Enhanced warfarin effect Increased anticoagulant sensitivity Increased anticoagulant sensitivity High sulfonamide blood levels Hypoglycemia	DIGITALIS		
Heparin	Polymyxin B	Incompatible in I.V. solution	Digitalis	Calcium Thiazide diuretic Reserpine Thyroxine	Digitalis toxicity Digitalis toxicity Bradycardia Decreased digitalis effect
ANTIDEPRESSANTS			DIURETICS		
MAO Inhibitors:	Alcohol Amphetamine Anesthetic (general)	Exaggerated alcohol effect Agitation, hypertensive crisis Enhanced central nervous system depression	Thiazine diuretics	Digitalis Hydralazine MAO inhibitor Mecamylamine Sulfonylurea	Digitalis toxicity Hypotension Hypotension Hypotension Aggravated glucose intolerance
Isonicotinic acid hydrazide	Anti-Parkinsonism agent	Increased anti-parkinsonism agent	ORAL HYPOGLYCEMICS		
Pargyline	(Other Hydrazine derivatives potentially)	Atropine-like poisoning	Sulfonylureas	Coumarin anticoagulant Phenylbutazone Sulfonamide Thiazide diuretic	Hypoglycemia Hypoglycemia Hypoglycemia Aggravated glucose intolerance
Barbiturate	Barbiturate	Enhanced sedation	SEDATIVES & TRANQUILIZERS		
Chloral hydrate	Chloral hydrate	Enhanced sedation	(See also barbiturates)	Chloral hydrate	Coumarin anticoagulant MAO inhibitor
Cocaine	Cocaine	Hypertension	Glutethimide	Coumarin anticoagulant	Decreased anticoagulant effect Enhanced sedation
Food or alcoholic beverage containing tyramine	Food or alcoholic beverage containing tyramine	Hypertensive crisis	Benzodiazepines	Alcohol Barbiturate MAO inhibitor Phenothiazine Tricyclic Antidepressant	Enhanced sedation Enhanced sedation Enhanced sedation Enhanced sedation Enhanced sedation, atropinism
Insulin	Insulin	Hypoglycemia	Phenothiazines	Alcohol Antihistamine Antihypertensive	Enhanced sedation Sedation, atropinism Increased hypotension (especially postural)
Meperidine	Meperidine	Hypertension or hypotension, enhanced central nervous system, effects depressed respiration	Barbiturate	Barbiturate	Enhanced sedation
Methyldopa	Methyldopa	Excitation, hypertension	MAO inhibitor	MAO inhibitor	Extrapyramidal reactions, hypertension
Chlordiazepoxide, diazepam	Chlordiazepoxide, diazepam	Enhanced sedation	Meperidine	Meperidine	Enhanced sedation, respiratory depression
Imipramine	Imipramine	Atropinism: excitation, coma, tremor, sweating, fever, delirium, seizures, rigid	Morphine	Morphine	Enhanced sedation, analgesia
Phenothiazine	Phenothiazine	Extrapyramidal reaction, hypertension	Reserpine	Reserpine	Hypotension
Reserpine	Reserpine	Excitation	Thiazide diuretic	Thiazide diuretic	Hypotension
Sympathomimetic	Sympathomimetic	Hypertensive crisis	Tricyclic Antidepressant	Tricyclic Antidepressant	Hypotension, atropinism, seizures
Thiazide diuretic	Thiazide diuretic	Hypotension	STEROIDS		
MAO inhibitors	MAO inhibitors	Agitation, tremor, opisthotonos, coma, fever	Estrogen/progesterone	Phenobarbital	Decreased estrogen/progesterone (in animals)
Tricyclic antidepressants:			Hydrocortisone	Antihistamine Barbiturate Diphenylhydantoin	Decreased hydrocortisone effect Decreased hydrocortisone effect Decreased hydrocortisone effect
Amitriptyline	Guanethidine	Hypertension, loss of antihypertensive action	Norethandrolone	Anticoagulant	Increased anticoagulant effect
Desipramine	Benzodiazepines	Atropinism	Methandrostenedione	Oxyphenbutazone	Increased oxyphenbutazone effect
Imipramine	MAO inhibitors	Severe atropine-like toxicity	ANTIHISTAMINES		
Nortriptyline		Atropinism, hypotension	Alcohol	Alcohol	Central nervous system depression
			Sedatives	Sedatives	Central nervous system depression
			Steroid (androgens, progesterone)	Steroid (androgens, progesterone)	Decreased steroid effect
			MAO inhibitor	MAO inhibitor	Increased antihistamine sedation, atropinism
			Parasympatholytics	Parasympatholytics	Increased parasympatholytic effect, atropinism
			Phenothiazine	Phenothiazine	Additive effect sedation, atropinism
			Reserpine	Reserpine	Sedation, atropinism

TABLE 4.—Influence of pH on Drug Absorption, Distribution, and Excretion

The diffusion of lipid soluble weak acids and bases depends in part upon their state of ionization in a given milieu. Ionized drugs diffuse across lipid rich cell membranes poorly. Intracellular sites are more acidic than plasma, hence alkaline drugs accumulate in cells. Other factors such as extensive protein binding, degree of lipid solubility, and partition coefficient may alter the predicted effect based upon pH of the drug alone.

Process	Drug A (Weak Acid)	Drug B (Weak Base)
Gastric absorption	Relatively rapid	Relatively slow
Small bowel absorption	Relatively slow	Relatively rapid
Plasma/Cell Ratio	Low	High
Renal clearance in:		
Acid Urine	Low	High
Alkaline Urine	High	Low
Examples:	Sulfonamides	Antihistamines
	Salicylic Acid	Mecamylamine
	Phenobarbital	Amphetamine

acidosis increases its plasma levels and may cause hypotension.⁴² Table 4 represents some commonly used drugs which are weak acid and bases.

Drug Interactions by Altered Renal Clearance

As pH may affect cellular distribution of a drug, so may urinary hydrogen ion concentration influence clearance of drugs by the kidney. Changes in urinary pH induced by disease—or as a result of therapy with ammonium chloride, sodium bicarbonate, thiazides or acetazolamide—may profoundly influence the renal excretion of many drugs that are weak acids or bases. Ionized drugs diffuse slowly across cell membranes and are slowly reabsorbed from the glomerular filtrate by the tubules; hence they are cleared relatively rapidly. Weak acids are reabsorbed poorly from an alkaline urine and weak bases are reabsorbed poorly from an acidic urine. Accordingly, weak acids such as phenobarbital and salicylic acid are rapidly cleared by the kidney during alkaline diuresis, while basic drugs such as amphetamine or mecamylamine would be cleared relatively slowly.⁴³

An interaction in the kidney may only be partially accounted for by alteration in renal clearance of the drug. For instance, salicylates may interfere with the uricosuric effects of probenecid by antagonistic action on the tubular sites of uric acid clearance but not by actually altering clearance of either drug. Likewise the ability of probenecid to delay the excretion of penicillin is due to a direct tubular effect of the former. Once again data must be carefully analyzed before interactions can be attributed solely to their competing renal

effects. When hypoglycemia occurred after phenylbutazone was added to a regimen using acetohexamide, clearance of the active metabolite hydroxyhexamide appeared diminished.⁴⁴ However, studies are needed to document this as the sole factor contributing to the hypoglycemia.

Interactions with the Psychotherapeutic Drugs

The phenothiazines are extremely useful in psychiatric disorders when patients require tranquilization. However, the effects they have on the central nervous system may predispose to potentiation of barbiturates, alcohol and narcotics. Complex changes in cardiovascular function are observed during administration of phenothiazines. Their central and peripheral effects may lead to postural hypotension. Because phenothiazines can block alpha receptors, the choice of drugs for the treatment of hypotension is limited. If the pressor used elicits both alpha and beta responses, the net effect during alpha receptor blockade could be beta mediated arterial dilation and, paradoxically, exaggerated hypotension.⁴⁵ If used with monamine oxidase inhibitors, phenothiazines may produce severe extrapyramidal reactions and hypertension.⁴⁶

Phenothiazines lower the seizure threshold, and when possible should be avoided in epileptic patients. This advice is particularly pertinent when the patients are taking other agents like the tricyclic antidepressants that also lower the seizure threshold. Phenothiazines have a quinidine-like action on myocardial conducting and pacemaking tissues. Ventricular tachycardia has been reported during phenothiazine therapy.⁴⁷ Treatment of such an arrhythmia should be similar to that used for quinidine toxicity, namely, induction of alkalosis, and/or use of isoproterenol, or electrical methods.⁴⁸ Use of cardiac depressant drugs like quinidine should be avoided.

The tricyclic antidepressants have largely supplanted the monamine oxidase inhibitors for treatment of depression. When they are given simultaneously with or shortly following administration of monamine oxidase inhibitors, severe atropine-like reactions may occur. Similar reactions may occur when the benzodiazepines are given with phenothiazines.⁴⁹ The benzodiazepines are relatively safe agents taken alone, but they potentiate the sedative and/or atropine-like effects of alcohol, barbiturates, phenothiazines and the tricyclic antidepressants. Monamine oxidase inhibitors also

TABLE 5.—*Oral Anticoagulant Interactions*

<i>Drug</i>	<i>Putative Mechanism</i>
<i>DIMINISHED Anticoagulant Effect:</i>	
Cholestyramine	Direct chemical
Vitamin K	Direct biochemical
Barbiturates	Decreased G-I absorption
Barbiturates	Enhanced metabolism
Glutethimide	Enhanced metabolism
Griseofulvin	Enhanced metabolism
Meprobamate	Enhanced metabolism
Diphenylhydantoin	Enhanced metabolism
Chloral Hydrate	Enhanced metabolism
Phenylbutazone (late)	Enhanced metabolism
Diazepam	Enhanced metabolism
Chlorpromazine	Enhanced metabolism
? Antihistamines	
? Chlordane, DDT	
<i>ENHANCED Anticoagulant Effect:</i>	
Aspirin	Direct biochemical
Propylthiouracil	Direct biochemical
Quinidine	Direct biochemical
Phenylbutazone (early)	Protein binding
Antibiotics	Decreased G-I flora
Oxyphenbutazone	Decreased metabolism
Phenylamidol	?
Dextrothyroxine	?
Levothyroxine	?
Clofibrate	?
Androsterone	?
<i>OTHER DRUG Enhanced:</i>	
Tolbutamide; Dicumarol	Protein binding
Dilantin; Dicumarol	?
Long acting Sulfas; Dicumarol	?

enhance the sedative effects of benzodiazepines.⁵⁰

Interactions of the psychotherapeutic agents with drugs of other categories has been recognized. Both phenothiazines⁵¹ and benzodiazepines alter the effects of oral anticoagulants.

Drug Interactions Conditioned by Previous Drug Effects or Disease

In some patients, drug toxicity is not produced by simple additive effects of drugs given simultaneously. Toxicity appears as a result of drug-induced changes in the patient. For example, thiazide diuretics, by producing potassium loss may predispose patients to digitalis toxicity. Likewise, reserpine, which depletes myocardial stores of norepinephrine, may cause undue bradycardia when digitalis is given.⁵² Catecholamine depleting agents like guanethidine and reserpine may render patients refractory to pressor agents that depend upon catecholamine release for their activity (mephentermine and metaraminol). Reserpine may also prevent uptake of administered catecholes into storage sites and thus may render patients hypersensitive to infused norepinephrine.⁵³ Propanolol inhibits beta sympathetic responses and has been blamed for lack of sympathetic response to

hypoglycemia caused by insulin or sulfonylureas.⁵⁴

Spontaneous variability of response to therapy during disease states can alter the relationship between simultaneously administered drugs. During hormonal replacement in patients with hypothyroidism, the dose of barbiturate sedatives and digitalis required to maintain a stable effect increases.⁵⁵ Conversely, thyroid replacement would promote a faster turnover of clotting factors and decrease the dose requirements of anticoagulant drugs.⁵⁶ Although the mechanism is not fully defined, administration of the antihyperlipemic drugs results in diminished requirements for oral anticoagulant drugs.⁵⁷ Antibiotic therapy which alters intestinal flora that normally synthesize vitamin K, reduces the prothombinopenic dose of warfarin. Certain antibiotic combinations, especially those involving the combination of a bacteriostatic with a bacteriocidal agent may be antagonistic. In most clinical settings the combinations can be avoided.⁵⁸ Spironolactone antagonizes the effects of aldosterone, and may result in hyperkalemia if potassium salts are given. This effect persists for several days after spironolactone is discontinued, as the initial onset of action of aldosterone is slow.

Conclusion

This review has emphasized the importance of drug interactions that can occur during administration of commonly used drugs. Other reviews are more complete.^{59,60,61} The recognized drug interactions for a single category of drugs, the oral anticoagulants, is given in Table 5. The list is long, and will undoubtedly lengthen. The current rate of publications in the drug interaction field is awesome. Two of the publications helpful in keeping current in this area are: *Clin-Alert* (published by Science Editors, Inc., P.O. Box 1174, Louisville, Kentucky 40202) and the Food and Drug Administration *Clinical Experience Abstracts* (D.H.E.W. Food and Drug Administration Bureau of Medicine, Medical Literature Branch, Washington, D.C. 20204) which summarize both individual drug reactions and drug interactions as they appear in the literature. Another library reference of use is Adverse Reaction Titles, Excerpta Medica Foundation, New York Academy of Medicine Building, 2 East 103rd Street, New York, N.Y. 10029.

The practitioner can avoid or detect interactions by continuing to be aware of their possibility, by avoiding multiple drug therapy when possible, and by carefully monitoring drug effects in his patients.

If evidence of enhanced or diminished drug activity is seen when a new drug is added to a therapeutic regimen, an interaction should be suspected until ruled out.

The number of drugs involved in interactions and their complex interplay with disease states will eventually require computer methods to store information about known interactions, and to prospectively predict potential drug interactions based upon information regarding the chemical and pharmacologic properties of the agents used in patients with given disorders. Awaiting this innovation, the physician must protect his patients by prudence in drug choice, and perspicacity during multiple drug therapy.

Appendix A is a summary of selected and potential (animal studies) drug interactions. Appendix B is a list of the generic and trade names of drugs mentioned in this review.

APPENDIX B

GENERIC AND TRADE NAMES OF DRUGS

ANALGESICS:

Aspirin (Salicylates) *Aspirin*®
 Meperidine *Demerol*®
 Phenylbutazone *Butazolidin*®
 Oxyphenbutazone *Tandearil*®

MUSCLE RELAXANTS:

Phenylramidol *Analexin*®

ANTIBIOTICS:

p-Aminosalicylic acid *PAS*®
 Chloramphenicol *Chloromycetin*®
 Griseofulvin *Fulvicin*®, *Grifulvin*®, *Grisactin*®
 Penicillin *Abbecillin*®, *Pentids*®, *Sugracillin*®, etc.
 Sulfonamides *Acusol*®, *Gantanol*®, etc.
 Long acting sulfonamide *Madribon*®
 Lincomycin *Lincocin*®
 Sulfaphenazole *Sulfabid*®
 Tetracycline *Achromycin*®, *Panmycin*®, *Sumycin*®, etc.
 Streptomycin *Streptomycin*®
 Neomycin *Mycifradin*®
 Polymyxin *Aerosporin*®
 Isoniazid *Niconyl*®, *Nicozide*®, *Nydradiz*®
 Methicillin *Staphcillin*®
 Sulfaethylthiadiazole *Sul-Spantab*®

ANTICOAGULANTS:

Coumarins:
 Bishydroxycoumarin *Dicumarol*®
 Ethyl biscoumaracetate *Tromexan*® ethylacetate
 Warfarin *Coumadin*®, *Panwarfin*®, *Prothromadin*®
 Phenprocoumon *Marcoumar*®, *Liquamar*®
 Acenocoumarin *Nicoumalone*®, *Sintrom*®
 Cyclocoumarol
 *Cumopyran*®, *Link Compound 63*, *Methopyranorin*®
 Heparin *Panheprin*® (sodium heparin)
 Protamine Sulfate *Protamine sulfate*®

ANTICONVULSANTS:

Diphenylhydantoin *Dilantin*®

ANTIDEPRESSANTS:

Monamine Oxidase Inhibitors:
 Pargyline *Eutonyl*®
 Tranlycypromine *Parnate*®

Amphetamines:
 Amphetamine *Benzedrine*®
 Methamphetamine *Desoxyephedrine*®, *Desoxyn*®, *Methidrine*®
 Tricyclic antidepressants:
 Imipramine *Tofranil*®
 Nortriptyline *Aventyl*®
 Amytriptyline *Elavil*®
 Desmethylinipramine *Norpramin*®

ANTIHYPERTENSIVES:

Guanethidine *Ismelin*®
 Alpha-methyl dopa *Aldomet*®
 Mecamylamine *Inversine*®
 Hydralazine *Apresoline*®
 Reserpine *Rauloydin*®, *Reserpoid*®, *Rau-sed*®, etc.

ADRENERGIC BLOCKING AGENTS:

Alpha:
 Phentolamine *Regitine*®
 Phenoxylbenzamine *Dibenzylamine*®
 Beta:
 Propranolol *Inderal*®

PRESSOR AGENTS:

Direct acting:
 Alpha stimulating, norepinephrine *Levophed*®
 Beta stimulating, isoproterenol *Isuprel*®
 Indirect acting:
 Metaraminol *Aramine*®
 Mephentermine *Wyamine*®

NEUROMUSCULAR BLOCKING AGENTS:

Decamethonium *C10*®, *Syncurine*®
 D-tubocurarine *Tubarine*®, *Tubadil*®
 Gallamine *Flaxedil*®
 Succinylcholine chloride *Diacetylcholine*® chloride, *Anectine*®, *Suxamethonium*®, etc.

PARASYMPATHETIC AGENTS:

Edrophonium *Tensilon*®
 Neostigmine *Prostigmine*® bromide
 Atropine *Atropine*®

ANTINEOPLASTIC AGENTS:

6-Mercaptopurine *Purinethol*®
 Methotrexate *Amethopterin*®
 Procarbazine *Natulan*®

ANTIMALARIALS:

Quinacrine *Mepacrine*®, *Atabrine*®, *Atebrin*®
 Pamaquine *Aminoquin*®, *Deprochin*®, *Plasmaquin*®
 Quinine *Quinamm*®
 Pyrimethamine *Daraprim*®

SEDATIVES:

Phenobarbital *Luminal*®, *Talpheno*®
 Chloral hydrate *Noctec*®, *Dormal*®, etc.
 Gluthethamide *Doriden*®
 Meprobamate *Equanil*®, *Miltown*®

BENZODIAZEPINES:

Chlordiazepoxide *Librium*®
 Diazepam *Valium*®
 Oxazepam *Serax*®

PHENOTHIAZINES:

Chlorpromazine *Thorazine*®, *Largactil*®, *Megaphen*®
 Promazine *Sparine*®
 Trifluoperazine *Vesprin*®
 Fluphenazine *Permitil*®, *Proxlixin*®
 Prochlorperazine *Campazine*®
 Trifluoperazine *Stelazine*®
 Thioridazine *Mellaril*®

ANTHYPERLIPEMIC DRUGS:

D-thyroxine *Choloxin*®
 Clofibrate *Atromid-S*®
 Androsterone *Atromid*®

DIURETIC AGENTS:

Spironolactone	<i>Aldactone</i> ®
Acetazolamide	<i>Diamox</i> ®
Benzothiadiazides: (Thiazides)	
Chlorothiazide	<i>Diuril</i> ®
Hydrochlorothiazide	<i>Oretic</i> ®, <i>Hydrodiuril</i> ®, <i>Esidrix</i> ®
Flumethazide	<i>Ademol</i> ®
Hydroflumethazide	<i>Saluron</i> ®
Bendroflumethazide	<i>Naturetin</i> ®
Benzthiazide	<i>Naclex</i> ®, <i>Exna</i> ®
Trichlormethiazide	<i>Naqua</i> ®, <i>Metahydrin</i> ®
Methyclothiazide	<i>Enduron</i> ®
Polythiazide	<i>Renese</i> ®
Cyclopenthiiazide	<i>Navidrex</i> ®
Cyclothiazide	<i>Anhydron</i> ®

HYPOGLYCEMIC AGENTS:

Sulfonylureas:	
Tolbutamide	<i>Orinase</i> ®
Chlorpropamide	<i>Diabinese</i> ®
Tolazamide	<i>Tolinase</i> ®
Insulin	

HORMONES:

Cortisol	<i>Cortisol</i> ®, <i>Cortef</i> ®, <i>Hydrocortisone</i> ®, <i>Solucortef</i> ®, etc.
Norethandrolone	<i>Nilevar</i> ®
Progesterone	<i>Progesterone</i> ®
Estrogens	<i>Esteed</i> ®, <i>Estinyl</i> ®, etc.
Thyroid	<i>Armour</i> ® thyroid, <i>Cytomel</i> ®, <i>Synthroid</i> ®, etc.

OTHER:

Digitalis	<i>Crystodigin</i> ®, <i>Digoxin</i> ®, <i>Purodigin</i> ®, etc.
Quinidine	<i>Quinidex</i> ®, <i>Quinora</i> ®, etc.
Cholestyramine	<i>Cuemid</i> ®
Kaolin	<i>Kaopectate</i> ®, etc.
Probenecid	<i>Benemid</i> ®
Allopurinol	<i>Zyloprim</i> ®
Ethylenediaminetetracetate	<i>EDTA</i> ®, <i>Versene</i> ®, <i>Edathamil</i> ®
Sulfinpyrazone	<i>Anturane</i> ®

ANTI-HISTAMINES:

Ethylenediamines:	
Antazoline	<i>Antistine</i> ®
Chloromethapyrilene citrate N.F.	<i>Chlorothen</i> ®, <i>Tagathen</i> ®
Clemizole HC1 N.N.D.	<i>Allecur</i> ®, <i>Reactrol</i>
Methaphenilene HC1	<i>Diatrine</i> ®
Methapyrilene HC1 N.F.	<i>Histadyl</i> ®, <i>Thenylene</i> ®, <i>Semikon</i> ®
Pyrilamine maleate (mepyramine, pyranisamine) U.S.P.	<i>Neo-Antergen</i> ®, <i>Paramal</i> ®, <i>Stangen</i> ®, <i>Thylogen</i> ®
Thenylidamine HC1 N.F.	<i>Thenfadi</i> ®
Thonzylamine HC1 N.F.	<i>Anahist</i> ®, <i>Neohetramine</i> ®
Tripeleannamine HC1 U.S.P.	<i>Pyribenzamine</i> ®

Amino Alkyl Ethers:

Bromodiphenhydramine HC1	<i>Ambodryl</i> ®, <i>Bromo-Benadryl</i> ®
Carbinoxamine maleate N.F.	<i>Clistin</i> ® (<i>d-isomer</i> , <i>Twiston</i> ®)
Diphenhydramine HC1 U.S.P.	<i>Benadryl</i> ®
Diphenylpyraline HC1 N.N.D.	<i>Diafen</i> ®, <i>Hispril</i> ®
Doxylamine succinate U.S.P.	<i>Decapryn</i> ®

Alkylamines:

Brompheniramine maleate N.F.	<i>Dimetane</i> ® (<i>d-isomer</i> , <i>Disomer</i> , <i>N.N.D.</i>)
Chlorpheniramine maleate U.S.P.	<i>Chlortrimeton</i> ® (<i>d-isomer</i> <i>Polaramine</i> ®, <i>N.N.D.</i>)
Dimethindene maleate N.N.D.	<i>Forhistal</i> ®
Pheniramine maleate N.F.	<i>Trimeton</i> ®
Pyrrobutamine phosphate N.N.D.	<i>Pyronil</i> ®
Triprolidine HC1 N.N.D.	<i>Actidil</i> ®

Piperazines:

Buclicline HC1	<i>Sofran</i> ®
Cyclizine HC1 U.S.P.	<i>Marezine</i> ®
Chlorcyclizine HC1 U.S.P.	<i>Di-Paralene</i> ®, <i>Perazil</i> ®
Meclizine HC1 U.S.P.	<i>Bonine</i> ®

REFERENCES

- Lasagna, L.: Drug toxicity in man: The problem and the challenge, *Ann. N.Y. Acad. Sci.*, 123:312-315, 12 Mar. 1965.
- Vere, D. W.: Errors of complex prescribing, *Lancet*, 1:370-373, 13 Feb. 1965.
- Simmons, M., Parker, J. M., Gowdy, C. W., and Coulter, W. K.: Adverse drug reactions during hospitalizations, *Canad. Med. Assn. J.*, 98:175, 20 Jan. 1966.
- Smith, J. W., Seidl, L. G., and Cluff, L. E.: Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility, *Ann. Intern. Med.*, 65:629-640, Oct. 1966.
- Modell, W.: Hazards of new drugs, *Science*, 139:1180-1185, 22 Mar. 1963.
- Motulsky, A. G.: The genetics of abnormal drug responses, *Ann. N.Y. Acad. Sci.*, 123:167-177, 12 Mar. 1965.
- Weiner, I. M., Washington, J. A., II, and Mudge, G. H.: On the mechanism of action of probenecid on renal tubular secretion, *Bull. Johns Hopkins Hosp.*, 106:33-46, June 1960.
- Aggeler, P. M., O'Reilly, R. A., Leong, L., and Kowitz, P. E.: Potentiation on anticoagulant effect of warfarin by phenylbutazone, *New Eng. J. Med.*, 276:496-501, 2 Mar. 1967.
- Hoffbrand, B. I., and Kininmonth, D. A.: Potentiation of anti-coagulants, *Brit. Med. J.*, 2:838-839, 24 June 1967.
- Conney, A. H., Jacobson, M., and Schneidman, K.: Induction of liver microsomal cortisol 6 β -hydroxylase by diphenylhydantoin or phenobarbital: An explanation for the increased excretion of 6-hydroxycortisol in humans treated with these drugs, *Life Sci.*, 4:1091-1098, May 1965.
- Dollery, C. T., Pentecost, B. L. and Samaan, N. A.: Drug induced diabetes, *Lancet*, 2:735-737, 13 Oct. 1962.
- Dearborn, E. H., Litchfield, J. T., Jr., Eisner, H. J., Corbett, J. J. and Dunnett, C. W.: The effect of various substances on the absorption of tetracycline in rats, *Antibiot. Med. Clin. Ther.*, 4:627, Oct. 1957.
- Council on Drugs: An antipruritic agent for primary biliary cirrhosis and cholestatic jaundice. Cholestyramine resin (Cuemid), *JAMA*, 197:261-262, 25 July 1966.
- Wagner, J. G.: Biopharmaceutics: Absorption aspects, *J. Pharm. Sci.*, 50:539-587, May 1961.
- Aggeler, P. M., and O'Reilly, R. A.: The pharmacological basis of oral anticoagulant therapy, *Thromb. Diath. Haemorrh. Suppl.*, 21:227-256, 1966.
- Pelissier, N. A., and Burgee, S. L., Jr.: Guide to incompatibilities, *Hosp. Pharm.*, 3:15-32, Jan. 1968 (104 incompatible drugs cited, some of these being incompatible with as many as 20 other drugs).
- Hogben, C. A. M., Tocco, D. J., Brodie, B. B., and Schanker, L. S.: On the mechanism of intestinal absorption of drugs, *J. Pharmacol. Exp. Ther.*, 125:275-282, April 1959.
- Wishinsky, H., Glasser, E. J., and Perkal, S.: Protein interactions of sulfonylurea compounds, *Diabetes*, 11, Suppl., 18-25, 1962.
- Dixon, R. L., Henderson, E. S., and Rall, D. P.: Plasma protein binding of methotrexate and its displacement by various drugs, *Fed. Proc.*, 24:454, Mar.-Apr. 1965.
- Zubrod, C. G., Kennedy, T. J., and Shannon, J. A.: Studies on the chemotherapy of human malaria. VIII. The physiological disposition of pamaquine, *J. Clin. Invest.*, 27:114-120, May 1948.
- Blount, R. E.: Management of chloroquin-resistant falciparum malaria (personal communication addendum), *Arch. Int. Med.*, 119:557-560, June 1967.
- O'Dell, G. B.: Studies in Kernicterus. I. The protein binding of bilirubin, *J. Clin. Invest.*, 38:823-833, May 1959.
- Silverman, W. A., Andersen, D. H., Blane, W. A., and Crozier, D. N.: A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens, *Pediatrics*, 18:614-625, 1956.
- Oates, J.: Personal communication.
- Leishman, A. W. D., Mathews, H. L., and Smith, A. J.: Antagonism of guanethidine by imipramine, *Lancet*, 1:112, 12 Jan. 1963.
- Vital Brazil, O., and Corrado, A. P.: The curariform action of streptomycin, *J. Pharmacol. Exp. Ther.*, 120:452-459, Aug. 1957.
- Koelle, G. B.: Neuromuscular blocking agents in Goodman, L. S., and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, ed. 3, The Macmillan Company, New York, 1965, pp. 596-613.
- Burns, J. J., and Conney, A. H.: Enzyme stimulation and inhibition in the metabolism of drugs, *Proc. Roy. Soc. Med.*, 58:955-960, Nov. 1965.
- van Dam, E. E., Overkamp, M., and Haanen, C.: The interaction of drugs, *Lancet*, 2:1027, 5 Nov. 1966.
- Cullen, S. I., and Catalano, P. M.: Griseofulvin-Warfarin antagonism, *JAMA*, 199:582-583, 20 Feb. 1967.
- Cucinell, S. A., Conney, A. H., Sansur, M., and Burns, J. J.: Drug interactions in man. I. Lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol®) and diphenylhydantoin (Dilantin®), *Clin. Pharm. Ther.*, 6:420-429, July-Aug. 1965.

32. Cucinell, S. A., Odessky, L., Weiss, M., and Dayton, P. G.: The effect of chloral hydrate on bishydroxycoumarin metabolism. A fatal outcome, *JAMA*, 197:366-368, 1 Aug. 1966.
33. Fox, S. L.: Potentiation of anticoagulants caused by pyrazole compounds, *JAMA*, 188:320-321, 20 Apr. 1964.
34. Elias, R. A.: Effect of various drugs on anticoagulant dosage in Nichol, E. S., Chairman, Editorial Board: *Anticoagulant Therapy in Ischemic Heart Disease*, Grune and Stratton, New York, 1965, p. 443.
35. Elion, G. B., Callahan, S., Nathan, H., Bieber, S., Rundles, R. W., and Hitchings, G. H.: Potentiation by inhibition of drug degradation: 6-substituted purines and xanthine oxidase, *Biochem. Pharmacol.*, 12:85-93, Jan. 1963.
36. DeConti, R. C., and Calabresi, P.: Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease, *New Eng. J. Med.*, 274:481-486, 3 Mar. 1966.
37. Kristensen, M., and Hansen, J. M.: Potentiation of the tolbutamide effect by Dicumarol, *Diabetes*, 16:211-214, April 1967.
38. Hansen, J. M., Kristensen, M., Skovsted, L., and Christensen, L. K.: Dicumarol-induced diphenylhydantoin intoxication, *Lancet*, 2:265-226, 30 July 1966.
39. Horwitz, D., Lovenberg, W., Engelman, K., and Sjoerdsma, A.: Monamine oxidase inhibitors, tyramine, and cheese, *JAMA*, 188:1108-1110, 29 June 1964.
40. Sjoqvist, F.: Psychotropic drugs (2) Interaction between monamine oxidase (MAO) inhibitors and other substances, *Proc. Roy. Soc. Med.*, 58:967-978, Nov. 1965.
41. Waddell, W. J., and Butler, T. C.: The distribution and excretion of phenobarbital, *J. Clin. Invest.*, 36:1217-1226, Aug. 1957.
42. Payne, J. P., and Rowe, G. G.: The effects of mecamlamine in the cat as modified by the administration of carbon dioxide, *Brit. J. Pharmacol.*, 12:457-460, Dec. 1957.
43. Milne, M. D.: Influence of acid-base balance on efficacy and toxicity of drugs, *Proc. Roy. Soc. Med.*, 58:961-963, Nov. 1965.
44. Field, J. B., Ohta, M., Boyle, C., and Remer, A.: A potentiation of acetohexamide hypoglycemia by phenylbutazone, *New Eng. J. Med.*, 277:889-894, 26 Oct. 1967.
45. Inglis, J. M., and Barrow, M. E. H.: Premedication, a reassessment, *Proc. Roy. Soc. Med.*, 58:29-32, Jan. 1965.
46. Barsa, J., and Saunders, J. C.: A comparative study of tranylcypromine and pargyline, *Psychopharmacologia*, 6:295-298, 14 Oct. 1964.
47. Shoonmaker, F. W., Osreen, R. T., and Greenfield, J. C., Jr.: Thioridazine (Mellaril®)-induced ventricular tachycardia controlled with an artificial pacemaker, *Ann. Int. Med.*, 65:1076-1078, Nov. 1966.
48. Selzer, A., and Wray, H. W.: Quinidine Syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias, *Circulation*, 30:17-26, July 1964.
49. Jarvik, M. E.: Drugs used in the treatment of psychiatric disorders in Goodman, L. S. and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, ed. 3, The Macmillan Company, New York, 1965, pp. 159-214.
50. Ibid.
51. Weiner, M.: Effect of centrally acting drugs on the action of coumarin anticoagulants, *Nature*, 212:1599-1600, 31 Dec. 1966.
52. Roberts, J., Ito, R., Reilly, J., and Cairoli, V. J.: Influence of reserpine and beta TM 10 on digitalis induced ventricular arrhythmia, *Circ. Res.*, 13:149-158, Aug. 1963.
53. Dollery, C. T.: Physiological and pharmacological interactions of antihypertensive drugs, *Proc. Roy. Soc. Med.*, 58:983-987, Nov. 1965.
54. Abramson, E. A., Arky, R. A., and Woeber, K. A.: Effects of propranolol on the hormonal and metabolic response to insulin-induced hypoglycemia, *Lancet*, 2:1386-1388, 24 Dec. 1966.
55. Lowenthal, I., and Fisher, L. M.: The effect of thyroid function in the prothrombin time response to warfarin in rats, *Experientia (Basel)*, 13:253-254, 15 June 1957.
56. Doherty, J. E., and Perkins, W. H.: Digoxin metabolism in hypo- and hyperthyroidism, studies with tritiated digoxin in thyroid disease, *Ann. Int. Med.*, 64:489-507, March 1966.
57. Schrogie, J. J., and Solomon, H. M.: The anticoagulant response to bishydroxycoumarin. II. The effect of D-thyroxine, clofibrate, and norethandrolone, *Clin. Pharmacol. Ther.*, 8:70-77, Jan.-Feb. 1967.
58. Jawetz, E.: The use of combinations of antimicrobial drugs, *Ann. Rev. Pharmacol.*, 8:151-170, 1968.
59. Symposium Number 7: Clinical effects of interactions between drugs. Chairman: The Rt. Hon. Lord Cohen of Birkenhead, *Proc. Roy. Soc. Med.*, 58:943-999, Nov. 1965.
60. McIver, A. K.: Drug interactions, *Pharm. J.*, 199:205-210, 2 Sept. 1967.
61. Gillette, J. R.: Theoretical aspects of drug interactions in Siegler, P. E. and Moyer, J. H., III: *Animal and Clinical Pharmacological Techniques in Drug Evaluation*, Year Book Medical Publishers, Chicago, 1967, pp. 48-66.

ATYPICAL CELLS IN G.I. ULCERATIVE DISEASE

"Considering our present knowledge of cells, cytologic examination is not specific for the diagnosis of ulcerative disease of the gastrointestinal tract. The results may be suggestive; and atypical cells may disappear in some instances when the patient improves (this is particularly true with chronic ulcerative colitis). These findings seem to make the technique of limited practical value. However, a knowledge of the atypical cells which may be seen in ulcerative diseases of the gastrointestinal tract is of more value to the cytologist in the careful cytologic examination for the presence of carcinoma. An appreciation of the possible significance of these cells may prevent the making of a false-positive cytodagnosis."

—NELSON D. HOLMQUIST, M.D., New Orleans
Audio-Digest Internal Medicine, Vol. 15, No. 18

MEDICAL STAFF CONFERENCE

Tuberculosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. YOUNG:* The patient was a 39-year-old Negro male who had been admitted to the San Francisco General Hospital with chief complaint of jaundice. He had been well until two months before, when he experienced right pleuritic pain in the chest, hemoptysis and fever. He was in hospital for four weeks with a diagnosis of pneumococcal pneumonia. A tuberculin skin test (intermediate strength, 5 TU) was positive with 20 mm of induration. There was no history of previous skin testing or exposure to tuberculosis. Serial x-ray films of the chest demonstrated progressive clearing of a right lower lobe infiltration without other evidence suggestive of tuberculosis. Three sputum smears were negative for acid fast bacteria. Because of the sizable skin reaction to intermediate strength tuberculin, both isoniazid, 300 mg twice daily and para-aminosalicylic acid, 6 gm twice daily, were prescribed and the patient was discharged from the hospital.

He was seen in a local clinic one month after discharge with a complaint of "not feeling well." Tetracycline was given because he was febrile. One week later he was readmitted to San Francisco General Hospital with complaint of general fatigue, weakness, anorexia, abdominal pain and jaundice. He denied the use of alcohol or medications other than those prescribed.

On physical examination he was observed to be disoriented, lethargic and obviously icteric.

Blood pressure was 130/80 mm of mercury, pulse rate 88 and respirations 24 per minute. No abnormalities were noted on examination of the chest and heart. The abdomen was flat, soft and not tender, but the liver could be felt 2 cm below the right costal margin. Except for the mental state of the patient, the results of neurological examination were within normal limits.

At the time of admission to hospital the following results of laboratory studies were reported: Hematocrit 44 percent, leukocytes 7,300 per cu mm, total protein 8 gm per 100 ml (equally divided between albumin and globulin), total bilirubin 18.8 mg per 100 ml (with 7.8 mg per 100 ml direct), serum glutamic oxaloacetic transaminase (SGOT) 1,030 units, and prothrombin time 10 percent of control.

All medications were discontinued but the patient declined from lethargy and confusion into frank coma with evidence of progressive hepatic insufficiency. Ascites developed, with abdominal distention and gastrointestinal bleeding. Despite plasmapheresis and administration of dexamethasone, the patient's condition deteriorated and he died after a period of hypotension.

Postmortem examination showed massive necrosis of the liver of the "viral hepatitis type." It could not be determined whether this was due to viral infection or to drug reaction. Granulomas found in the liver and lung were believed to represent healing lesions, presumably resulting from infection with tubercle bacillus.

*Donald Young, M.D., USPHS Postdoctoral Fellow, Supported by Training Grant HE-05705.

DR. SMITH:* Dr. Youker, will you demonstrate the x-ray findings.

DR. YOUKER:† A film of the chest taken 8 November shows an area of consolidation in the right lower lung which obliterates the right heart border. There is probably atelectasis of the left base and spotty areas of infiltration behind the heart. There is some prominence of the minor lobe fissure due either to fluid or to pleural reaction. An azygous lobe fissure is nicely demonstrated.

A film taken 16 January, the time of the second hospital admission, shows that these processes have largely cleared except for residua at the right base. There is persistent obliteration of the right heart border. There is a little apical pleural thickening but no other evidence of apical disease.

The final film is just that—a terminal film. It shows an endotracheal tube in place and almost complete obliteration of the left lung owing to lack of aeration, either from aspiration or from cardiac failure and pulmonary edema. Similar changes, although not quite as pronounced, are seen on the right side.

In summary, the x-ray films reveal the course of a patient who when first examined had an area of pneumonia, most striking on the right but with changes on the left as well. Considerable clearing of these lesions followed, but subsequently a terminal illness characterized by diffuse pulmonary infiltrates.

DR. SMITH: The discussion on this patient will be opened by Dr. John Murray who is Chief of the Chest Service at the San Francisco General Hospital.

DR. MURRAY:‡ I was a little surprised when asked to discuss tuberculosis at this conference. Since we had over 400 patients admitted to San Francisco General Hospital last year for either active or suspected tuberculosis, the disease is so much a part of our daily life that it hardly seemed a suitable subject for Grand Rounds. In thinking about the problem, however, I realized that a number of significant changes have occurred in the past few years in our philosophy about the treatment of tuberculosis. One of the most important developments has been the discovery that significant clinical tuberculosis can be prevented by

*Lloyd H. Smith, Jr., M.D.: Professor and Chairman, Department of Medicine.

†James Youker, M.D.: Assistant Professor of Radiology.

‡John Murray, M.D.: Associate Professor of Medicine.

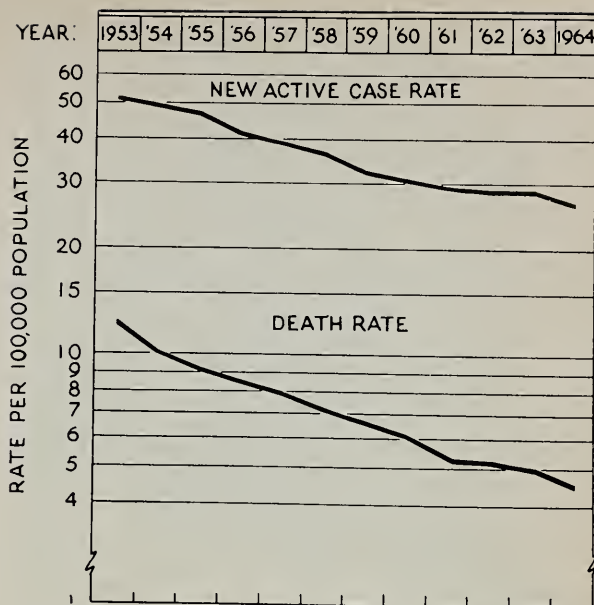


Chart 1.—The new active case rate and the death rate from tuberculosis in the years 1953 to 1964. (Data from U.S. Public Health Service Publication No. 638.)

means of chemotherapy. Based on these observations, criteria have been suggested for the selection of patients for chemoprophylaxis.^{1,2} The case history presented today was chosen to show both the potential rewards as well as the hazards of this approach to the treatment of tuberculosis.

Tuberculosis is still an important medical problem, as is demonstrated in Chart 1, which shows data on the incidence of new cases and the death rate during a recent decade. There has been a decrease in both new active cases and deaths, but the decline in the death rate has been greater than the decline in the incidence of new cases. Moreover, since the nation's population is increasing, the total number of new cases of tuberculosis that are diagnosed in the United States each year has decreased only slightly. The death rate in 1966 was 4.1 per 100,000; in the year 1900 the death rate was 300 per 100,000, and tuberculosis was the most common cause of death. In the early 1950's when the death rate was 22.9 per 100,000, it was the seventh most common cause of death in the United States. Now it is the twentieth. I think it is worth emphasizing, however, that tuberculosis still remains the most common infection that causes death, not only in the United States but in the entire world. The prevention and chemoprophylaxis of tuberculosis, therefore, are relevant and important medical considerations.

Figure 1 demonstrates the usual way that tuberculosis begins in the body; it shows part of a

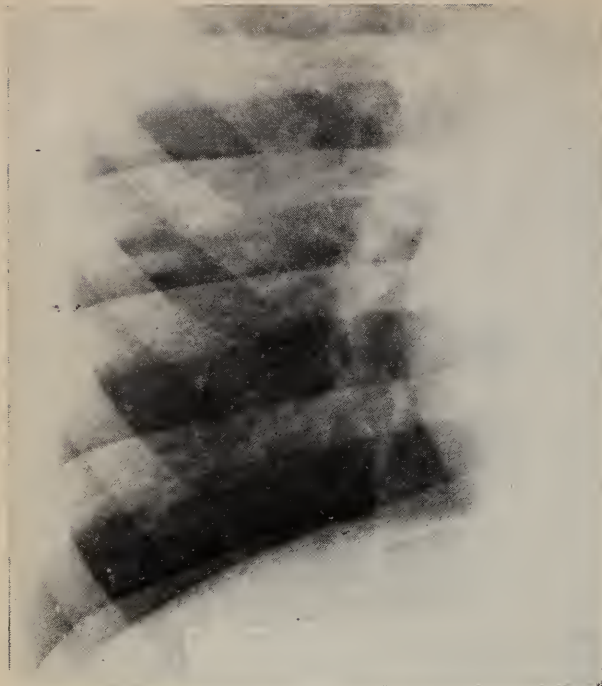


Figure 1.—Detailed x-ray view of the right lower lobe of a young girl taken 25 May 1959. A small but definite infiltration is present (compare with Figure 3).

thoracic x-ray film of a young girl taken in May of 1959 because she had been in contact with a person who had active tuberculosis. The lesion that you see in the interspace was overlooked and the patient was not treated, even though the tuberculin skin test was positive. This would not occur today.

Figure 2 shows the same patient in 1965. Now there is a small calcified lesion at the site of the previous infiltration. There are also some punctate areas of calcification in the hilar lymph nodes. This sequence represents the usual response of primary tuberculosis. We do not know exactly how many patients who acquire primary disease subsequently go on to have more significant clinical involvement. Available figures suggest the risk is of the order of magnitude of 5 to 10 percent. Therefore approximately 90 to 95 percent of patients who initially acquire primary tuberculosis will have spontaneous healing of lesions. Many of these patients will have no detectable residual lesions, but some will show calcifications in either the lung parenchyma (Ghon complex) or the hilar lymph nodes.

Five to 10 percent of patients do acquire more advanced forms of the disease which may be manifested in a variety of ways. Figure 3 shows an x-ray film of the chest of a patient with tuberculosis pleurisy with effusion, a condition that pre-



Figure 2.—Detailed x-ray view of the right lower lobe from the same patient shown in Figure 1, taken 24 June 1965. The previous infiltration has largely resolved, leaving a small calcified focus. In addition, there are calcifications in the hilar nodes.

sumably develops by retrograde extension in lymphatic channels from the primary lesion. Both the parietal and visceral pleura are ultimately involved and become covered with granulomatous lesions which cause the exudative reaction that is so characteristic of this form of the illness.

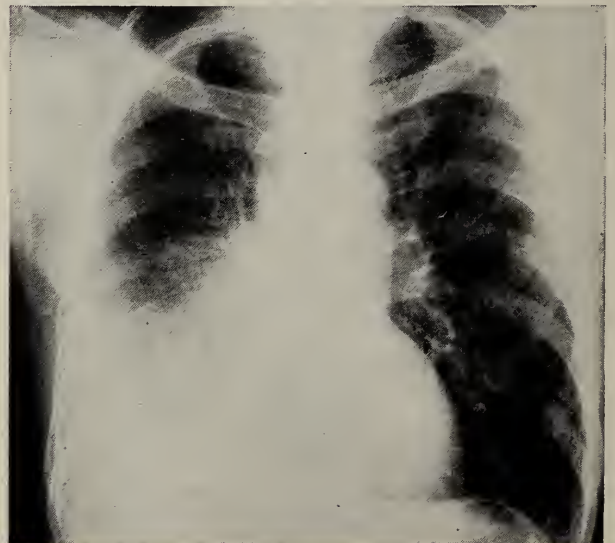


Figure 3.—X-ray film of chest of an adult male, showing a large right pleural effusion. Pleural biopsy revealed caseating granulomata and culture of the effusion yielded *M. tuberculosis*.

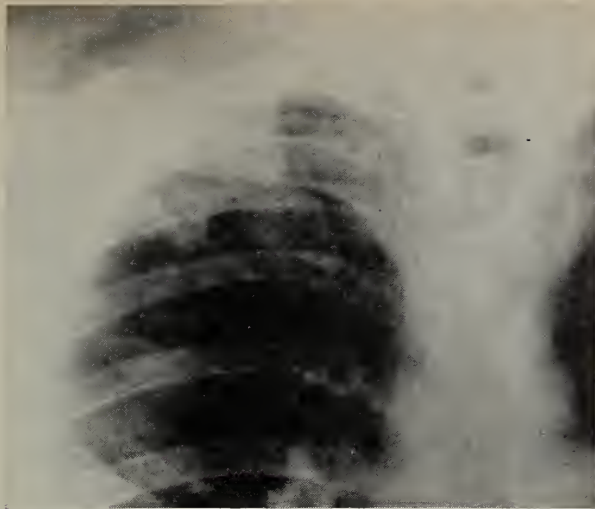


Figure 4.—Detailed x-ray view of right upper lobe of adult male patient with reinfection tuberculosis. The infiltration is in a characteristic location in the apical segment.

Reinfection tuberculosis is considered to include postprimary progression, reinfection and superinfection. This form of the disease characteristically localizes in the apical and posterior segments of the upper lobes as shown in Figure 4.

Figure 5 shows a more advanced kind of reinfection tuberculosis which has progressed to necrosis and cavity formation. In some patients the disease continues to progress and causes massive necrosis and cavity formation in both lungs. Tuberculosis is still encountered in this form today and may cause death before the disease is recognized. Nearly 1,800 cases a year are first diagnosed at autopsy examination after the death of the patient.

Hematogenous dissemination ensues if tubercle bacilli invade the bloodstream. A hematogenous component is part of most initial tuberculous infections but is usually adequately controlled by the body's responses. If defense mechanisms are faulty or massive distribution occurs, the lung fields become studded with tiny granulomatous lesions and produce changes that on x-ray films appear as of widespread involvement by uniform, discrete infiltrations that are characteristic of miliary tuberculosis (Figure 6). The lungs are not the only organ system involved in hematogenous dissemination. Numerous lesions can be found in the liver, which makes the organ an excellent site for biopsy material suitable for cultural and histological examinations.

The pathogenicity and infectivity of the tubercle bacillus probably have not changed in the past few centuries; once bacilli get into the body and before

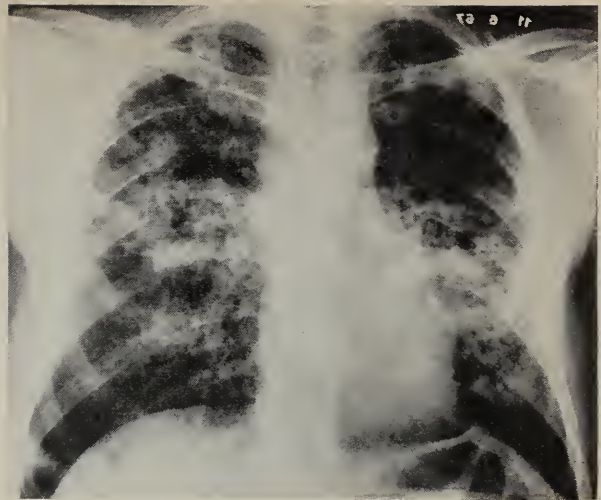


Figure 5.—X-ray film of chest of an adult male patient with far advanced tuberculosis. Extensive infiltrations and cavities are present in both lungs.

chemotherapy is begun, they behave in the traditional fashion. Epidemiologic features of the disease have changed, however. Previously tuberculosis was an important disease of infants, children and young adults. In the early 1900's it was unlikely that an individual would have reached the age of 25 or 30 without having a positive tuberculin reaction indicative of his having acquired tuberculosis. Today, tuberculosis in the United States is predominantly a disease of the older age groups—

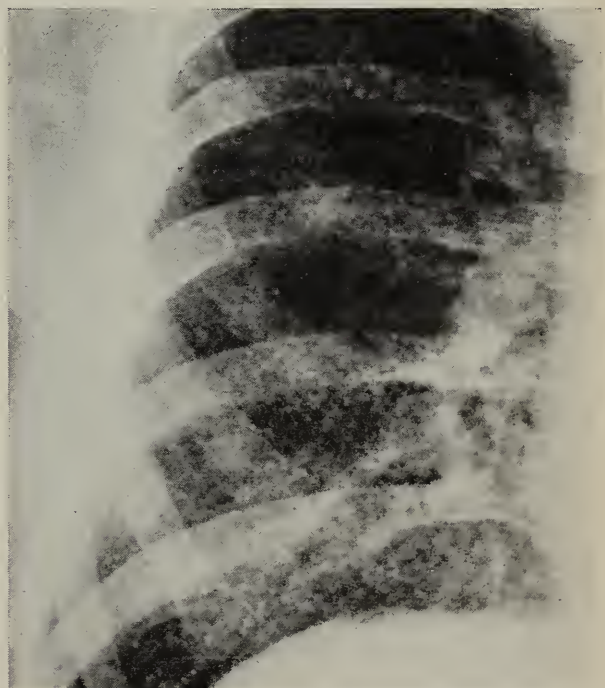


Figure 6.—Detailed x-ray view of the right lower lobe of adult male with miliary tuberculosis. Note the uniform characteristics of the widespread discrete infiltrates.

65 and over, the case rate there being three to four times greater than it is in infants and children.

This pattern has been well documented by recent skin test surveys which show a very low incidence of positive tuberculin skin tests in urban grade school children. There seems to be a definitely declining incidence of tuberculosis in young people while new active cases are found increasingly in older persons. These observations are important because they define the reservoir of active disease and indicate that most of the elderly who are discovered to have active tuberculosis probably have exacerbations of disease that was acquired ten to twenty years before, perhaps longer. Such persons, then, constitute an important target group for chemoprophylaxis.

In order to identify the presence of living tubercle bacilli in the body, we rely heavily upon the use of the tuberculin skin test. Induration indicates delayed hypersensitivity, but its significance depends upon the size of the indurated area. A skin test survey of one-half million Navy recruits recorded the intensity of reactions to standard purified protein derivative (PPD-S); these were divided into small reactions (induration 2 to 9 mm in diameter) and those of 10 mm or more.³ The results of this survey emphasize one important clinical point—skin tests should not be recorded as either positive or negative, but the area of induration should be measured and reported in the chart at both 48 and 72 hour intervals. This is required because the implications of the response vary with the size of the tuberculin reaction. For example, there are geographic variations in the incidence of small and large reactions. The southeastern United States is an area in which there is a high incidence of small reactions and a low incidence of large reactions. Presumably the reason for this is the common occurrence of subclinical infections with the Battey bacillus, one of the "atypical" mycobacterial organisms. The incidence of large tuberculin reactions to Battey antigen (PPD-B) is 60 to 70 percent in the southeastern United States. Presumably cross reaction between the shared antigens of PPD-S and PPD-B accounts for the smaller sized reactions to the PPD-S tuberculin. Cross reactions are clinically important because several atypical acid-fast organisms have been identified which have been classified into four groups: the photochromogens (Group I) which are prevalent in the midwestern United States, the Scotochromogens (Group II) which are present throughout the

country and which account for the highest incidence of skin test reactivity, the Battey-Avian group (Group III) which are common in the southeastern United States, and the rapid growers (Group IV) which are widespread in nature but unusual pathogens.

I think most chest physicians would regard a skin test response of greater than 10 mm as being definitely positive. A reaction in the range of 5 to 10 mm has several possible interpretations: (1) that sensitivity is developing but the skin test was performed at a moment when sensitivity was present but was not fully developed; (2) that sensitivity is waning from either loss of antigenic stimulus (death of organisms) or failure of antigenic responsiveness; and (3) that sensitivity represents cross reaction with other mycobacterial organisms. We believe that if a skin test response is within the 5 to 10 mm range, skin testing should be performed with "atypical" mycobacterial antigens; (these are now available in most chest clinics and Public Health Service dispensaries). If the patient can be shown to have a much stronger reaction to an antigen other than PPD-S he probably is not a candidate for chemoprophylaxis. This recommendation is based on the data shown in Table 1, obtained from subjects whose skin test response was between 6 and 11 mm. For persons who had a greater reaction to PPD-S than to PPD-B the risk was much higher that active tuberculosis would develop during the four-year observation period. When the response to PPD-S was less than the response to PPD-B, the rate of tuberculosis was very low. When the response to PPD-B was a very strong one, that is, greater than 11 mm, there was an even lower incidence of active tuberculosis (5 per 100,000) which suggests a prophylactic effect from the previous acquisition of "atypical" mycobacterial skin test sensitivity; this is probably a real phenomenon that is due to a BCG-like effect. Cross sensitization from atypical mycobacteria is believed to be one of the reasons for the decline in clinical tuberculosis that antedated the use of chemotherapy and Public Health control measures.

With the aid of tuberculin skin tests, groups

TABLE 1.—*Risk of Developing Active Tuberculosis During a Four Year Observation Period*

<i>Skin test reaction</i>	<i>Risk per 100,000</i>
PPD-S>PPD-B	242
PPD-S=PPD-B	102
PPD-S<PPD-B	19
PPD-B>11 mm	5

can be identified in which the high risk of developing active disease can be reduced by chemoprophylaxis. The American Thoracic Society has proposed guides for the selection of patients for chemoprophylaxis.^{1,2} Highest priority is given to patients who are known to have had tuberculosis but who have never been treated (or those who received an inadequate course of chemotherapy) even though they are believed to have inactive disease. As mentioned, this group seems to be the reservoir from which new cases develop. Consideration should be given to the treatment of persons who have positive skin tests and very suspicious chest x-ray findings. If someone has apical scarring or diffuse fibrotic lesions and a skin test response of greater than 10 mm in diameter, he would be included in this category and be a candidate for chemoprophylaxis. Since diminished sensitivity to tuberculo-proteins occurs with aging an older patient who is known to have had tuberculosis should be given chemotherapy if his tuberculin skin response exceeds even 5 mm.

There are a number of clinical situations in which the risk of the development of active tuberculosis in a patient with a positive skin test is substantially increased. Since this group of patients is at high risk, they should receive chemoprophylaxis. These are patients who are receiving corticosteroids, or who have had gastrectomy, or who have malignant disease of the reticuloendothelial system — particularly lymphoma and leukemia — or diabetes mellitus.

Other candidates for chemoprophylaxis are subjects in whom the tuberculin reaction converts from negative to positive. We are now recommending treatment of tuberculin “converters” regardless of age, although previously we recommended it only if they were children. Conversion of a tuberculin skin test indicates the recent acquisition of viable bacteria. Chemoprophylaxis has been shown to be effective in school children with positive skin tests, regardless of whether or not they are known converters.⁴ Previously the age for treatment of all positive reactors was three years, then it became five years and now it has been extended to age 20.² (Not only is the risk of the development of demonstrable active tuberculosis greater in young persons, if their disease progresses it is usually a fulminating and serious variety.)

The goal of therapy, according to the U.S. Public Health Service, is the treatment of all posi-

tive reactors. It is believed that this would “cure” the reservoir of infection within the United States. Incidentally, an effort has been made to eliminate bovine tuberculosis by both the treatment and the slaughter of all tuberculin-positive cows. This combination has proved quite effective in the control of the disease but it has not eradicated bovine tuberculosis in this country.

There are three other special circumstances which should be mentioned for completeness. One of these is the “contacts” of patients who have tuberculosis. They are the other exception to the rule that we treat only persons with tuberculin skin test responses greater than 10 mm. We recommend that all persons who have been in contact with patients with known active tuberculosis should be given chemoprophylaxis if their skin test reaction is greater than 5 mm. This modification is made in part because it is possible that their small reactions represent emerging skin test sensitivity.

If measles or whooping cough should develop in a child known to have had tuberculosis, chemoprophylaxis should be given, for the incidence of relapse of tuberculosis after such infections is high. In such circumstances therapy should be continued for two or three months if the patient was treated adequately before. If not, it should be given for a full year. Finally, a tuberculin-positive woman who is pregnant should have chemotherapy beginning in the last trimester and continuing for a full year.

Diagnostic culture of adequate sputum or gastric specimens for tubercle bacillus should be performed whenever possible. Specific identification with the niacin test and drug sensitivity studies will then be available, which will aid in the choice of the chemotherapeutic regimen, in determining the duration of therapy, and in deciding upon follow-up measures.

Table 2 lists the drug available for the treatment of tuberculosis. The whole concept of chemoprophylaxis was made possible by the availability of isoniazid, which is a relatively non-toxic, inexpensive drug that can be administered success-

TABLE 2.—Useful Drugs for Treating Tuberculosis

First Line Drugs	Second Line Drugs
Isoniazid	Ethambutal
Streptomycin	Ethionamide
Para-aminosalicylic acid	Cycloserine
	Pyrazinamide
	Viomycin
	Kanamycin
	Capreomycin

fully to outpatients. I would like to call your attention to two new drugs. One, ethambutal, has proved to be very efficacious and may have a role in chemoprophylaxis; it will certainly play a much more important role in the initial drug treatment of tuberculosis. The other, capreomycin, is still (1968) restricted by the Food and Drug Administration but appears to be approximately equal in effectiveness to streptomycin.

A comment is necessary concerning the use of BCG. It should be apparent from what has been said that the use of BCG would immensely complicate the problem of tuberculosis control by adding to the population a number of tuberculin-positive persons who could not readily be distinguished from those who were naturally infected. Although there is no doubt that BCG is an effective means of diminishing clinically significant tuberculosis, the United States Public Health Service and the National Tuberculosis Association have decided that the best available method for the eradication of tuberculosis as a major health problem in the United States is through the use of skin testing and the treatment of those who fall into the vulnerable category.

The decision was made to treat the patient under discussion today on the basis of his strongly positive (20 mm) skin test reaction. Because of his poor socioeconomic background and habits, he was considered to be liable to the development of significant tuberculosis in the future. Cultures were submitted to the laboratory for identification of tubercle bacilli and he was given isoniazid and para-aminosalicylic acid. Our plan was to continue treatment until the original cultures were reported; if they were negative we were going to maintain him on only one drug — isoniazid. Initially, however, therapy with two drugs was begun on the assumption that he might have more significant tuberculosis which would be detected by positive cultures. In such a situation, treatment with two drugs is mandatory. The patient was not kept in our observation and treatment, however, but was dealt with in another facility, where the decision was made to continue both agents. The contribution of the drugs, both of which are hepatotoxic, to his final illness is conjectural. We would be more certain about their role if they had been stopped when the patient first complained of symptoms of hepatitis. Physicians should be aware of the potential hazards of chemoprophylaxis and weigh the benefits to be obtained against the risks involved.

The patient undoubtedly had active tuberculosis and needed chemotherapy. Caseating granulomatous lesions were found in his liver and lungs at postmortem examination. One fluorescent stain was said to show acid-fast organisms. Although the culture of this lesion was negative, I believe this constitutes good evidence of tuberculosis.

DR. SMITH: Thank you very much, Dr. Murray. I think we should take time for any questions or comments.

PHYSICIAN IN AUDIENCE: Recently doctors at Letterman Army Hospital, San Francisco, have dealt with a number of soldiers with active tuberculosis who were all skin test negative. Diagnosis was confirmed by lung biopsy. How often do you run into this problem?

DR. MURRAY: It is difficult to provide statistics that satisfactorily answer the question. In one series the intermediate skin test was found to be positive in approximately 90 percent of patients with proven active disease.⁵ Known causes of skin test anergy are sarcoidosis, lymphoma, and severe debilitating disease.

The problem is discussed in a recent article which describes Navy recruits who also had negative skin test reaction in the presence of active disease.⁶ In patients the diagnosis was established not only by culture but also by biopsy techniques that were not widely used a few years ago. Physicians should recognize that the phenomenon exists and should not rely on a negative reaction to skin test to eliminate the possibilities of disease. For greater accuracy in excluding tuberculosis, when the intermediate skin test is negative a second strength PPD, which is 50 times more potent, should be applied.

QUESTION FROM THE AUDIENCE: How often do you recommend skin tests?

DR. MURRAY: I think this would depend upon the vulnerability of the group. Subjects who are in contact with patients who are known to have active tuberculosis should be skin tested at three to six month intervals. In the case of house staff and medical students, we are recommending that this be done at six-month intervals. In the population at large probably annual skin tests would be ideal, but that may not be practical. In San Francisco schools the children are routinely skin tested three times, in the first, seventh and twelfth grades. Also, children new to the San Francisco school

system are tested when entering. This testing has proved to be very valuable as a case-finding tool.

QUESTION FROM THE AUDIENCE: Is the dose weight adjusted in chemoprophylaxis?

DR. MURRAY: Yes. In children the recommended dose of isoniazid is up to 10 mg per kg of body weight, and in adults from 5 to 8 mg per kg, the total daily dose not to exceed 300 mg.

QUESTION FROM THE AUDIENCE: Will repeated skin testing itself cause conversion of the skin test?

DR. MURRAY: No.

DR. CARMAN:* I would like to emphasize one or two points made by Dr. Murray. One is that tuberculosis is important in the Bay Area and San

*Charles T. Carman, M.D.: Associate Professor of Medicine.

Francisco. The majority of the cases of tuberculosis in the United States are located in 11 seaport cities, of which San Francisco is an important one. I would also like to emphasize the importance of chemoprophylaxis if we are going to wipe out the reservoir of tuberculosis. We should take as our goal the virtual absence of new cases.

REFERENCES

1. American Thoracic Society Committee on Therapy: Preventive treatment in tuberculosis, *Am. Rev. Resp. Dis.*, 91:297, 1965.
2. American Thoracic Society Ad Hoc Committee: Chemoprophylaxis for the Prevention of Tuberculosis, *Am. Rev. Resp. Dis.*, 96:558, 1967.
3. Edwards, L. B.: Current status of the tuberculin test, *Annals New York Acad. Sci.*, 106:32, 1963.
4. Curry, F. J.: Prophylactic Effect of Isoniazid in Young Tuberculin Reactors. *New Eng. J. Med.*, 277:562, 1967.
5. Ledwith, J. W., and Gray, J. A. C.: The tuberculin reaction in patients admitted to a military tuberculosis service. 1958-1960, *Am. Rev. Resp. Dis.*, 84:268, 1961.
6. Kent, D. C., and Schwartz, R.: Active pulmonary tuberculosis with negative tuberculin skin reactions, *Am. Rev. Resp. Dis.*, 95:411, 1967.

WHEN MOTHERS NEGLECT GIVING PRESCRIBED IRON

"When young children (nine months to three years old) with hypochromic anemia are started on iron therapy and the anemia is not corrected, the most common cause is the parents' failure to administer iron. The mother herself (overworked—and understandably defensive, if the question is put directly to her) will more likely than not deny that she's been negligent in administering the iron. I have gained more helpful information in approaching the problem somewhat tangentially. You know that oral iron will invariably stain the teeth (this is a reversible staining) and that it also colors the stools quite black. If the unsuspecting mother admits that the stools have been their usual nice yellow color, and if you observe on physical examination that there is no dental staining, I think that you can conclude that the child has not been receiving the iron. Such a child may need parenteral iron to correct his iron deficiency."

—JOHN LUKENS, M.D., Columbia, Missouri
Audio-Digest, Pediatrics, Vol. 14, No. 15

The Short-Doyle Program

Past, Present and Future

WILLIAM B. BEACH, JR., M.D., AND ANNE DAVIS, *Sacramento*

THE GROWTH OF community psychiatric services in California has paralleled in a general fashion the development of similar services, where they exist, across the nation. California's public, tax-supported community mental health program, however, has become exceptionally active in recent years and shows every sign of continued expansion.

Before catching a bird's eye view of the development of these local mental health services and before discussing nearer than yesterday changes in the community program on a statewide level, let us clearly understand what local mental health services are.

"Community psychiatry" is a broad term encompassing psychiatric services of all types, through private as well as public resources, to a population within a given community.

"Local mental health services" as used in the context of this writing refers to public, tax-supported mental health programs engendered within a community for the benefit of the citizens of the community. Local mental health services are supported, at least in part, by local funds and are traditionally available to a person within a reasonable distance of his family home. Local mental health services are distinct from state mental health services, which are also tax-supported, but which are maintained solely by the State Department of

Mental Hygiene in a few large institutions scattered throughout California.

Background of the Short-Doyle Act

Until 1957 most public, tax-supported mental health services were provided in state hospitals and clinics operated by the Department of Mental Hygiene. "Community services" consisted largely of a few private, non-profit clinics and the available reservoir of private psychiatry. Individual psychiatrists and private hospital or clinic staff scattered throughout larger metropolitan communities provided care to citizens who were personally able to afford it and also to some who were not. A great many people unable to pay for the cost of their own treatment, however, ultimately entered a state hospital, either voluntarily or by court commitment.

Although there were several large state hospitals for the mentally ill scattered widely throughout California, many state hospital patients were far removed geographically from their homes during hospitalization. Isolation and mass regimentation which tended to prolong institutional treatment were generally considered undesirable, but seemed more like circumstantial necessities than remediable conditions.

In addition California state hospitals were experiencing a continual growth in patient population. The rate of admission to state hospitals for the mentally ill per 100,000 population, for instance, jumped from 106.6 in the year ended 30

Deputy Director, Division of Local Programs, California State Department of Mental Hygiene (Beach), and Community Program Analyst, California State Department of Mental Hygiene (Davis).

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Reprint requests to: Division of Local Programs, California State Department of Mental Hygiene, 1500-5th Street, Sacramento 95814 (Dr. Beach).

June 1948 to 139.0 during the year ended 30 June 1953. The overcrowding of state hospitals was becoming strikingly distressing. By the early 1950's the rate of growth for the mentally ill resident population in California state hospitals was close to 1,000 additional occupied beds per fiscal year. The prospect of adding 1,000 new beds each year throughout the state hospital system seemed to portend nothing but continual overcrowding of existing hospitals or the eventual construction of large new state hospitals as the population continued to grow.

It was during the years between 1950 and 1955 that legislators, responsible citizens and citizen associations, and the medical and psychiatric professions themselves began an intensive planning effort aimed at stemming the tide of state hospital growth, and also at hopefully eliminating some of the admittedly negative aspects of state hospital-type treatment. After considerable study on the part of such groups as the California Medical Association and the County Supervisors Association, a system for providing local mental health services was endorsed by the Department of Mental Hygiene and planned as a legislative proposal.

Although the proponents of the newly envisioned system of local mental health services believed at one point that they had cleared all legislative obstacles in 1955, it was not until 6 July 1957 that the bill was signed by the Governor and thereby enacted into law. Known as the Short-Doyle Act after Senator Alan Short and Assemblyman Donald Doyle, who guided it through the legislature, the new law provided a legal instrument or mechanism permitting local communities to develop mental health services through the use of state funds if they chose to do so.

Nature of the Short-Doyle Program

What is the Short-Doyle Act? What does it provide? And how did it effect changes in the total mental health and community mental health fields in California?

Basically the Short-Doyle Act provides state funds to be matched by local funds for the development of psychiatric and other mental health-related services at the local level. The community body appropriating funds for mental health services is usually County Government, although a few Short-Doyle city programs did develop following the passage of the Act.

The original state-local matching formula was

50-50; whatever sum the county (or city) appropriated for local mental health services, less fees, insurance and other minor charges, was exactly matched by the state and paid to the county under a reimbursement plan. The program of mental health services developed in any county, then, was partly financed by the county and partly by the state.

During the 11 years since the Short-Doyle Act became effective, legislative action has altered the state-local matching formula in favor of the county. A bill recently signed by the Governor during the 1968 Legislative Session provided for a 75 percent-25 percent matching formula for all Short-Doyle services, the state share being 75 percent and the county's 25 percent.

A local mental health program, commonly called a Short-Doyle program, is under the direction of a local mental health director who is a physician and frequently a psychiatrist. The program is locally based and locally operated, with the director and his staff being employees of the county or city whose population is served by the Short-Doyle program. However, since the state defrays a large portion of the expenses, the state, through the Department of Mental Hygiene, also maintains a regulatory control over the program.

The Short-Doyle Act specifically designated the type of mental health services that could be locally provided under the Short-Doyle plan. The original services, which were five in number, will be expanded to ten through the action of another remarkable piece of legislation to be discussed later. The five original services, which are still technically operative, are as follows:

1. Psychiatric outpatient treatment.
2. Psychiatric inpatient treatment in a general hospital or in a psychiatric hospital affiliated with a general hospital.
3. Rehabilitative services for the psychiatrically disabled.
4. Consultation by qualified mental health personnel to the professional staff of public and private agencies in the community.
5. Mental health information and education services to the public and to key professional groups.

Professional staffing of county Short-Doyle programs in California tends to follow the traditional mental health professional team concept of psychiatrist-psychologist-social worker, although psychiatric nurses, public health nurses, vocational rehabilitation therapists, student professional as-

sistants and other categories of personnel are also commonly hired. Inpatient wards are most frequently located in county hospitals, although several large programs maintain multiple contracts with private hospitals for services to Short-Doyle patients.

A county Short-Doyle program is frequently operated through the county hospital or through numerous hospitals, clinics and professional resources of a private nature in the community. In heavily populated counties with sophisticated Short-Doyle programs, services are usually diffused through the community and may be located in any number of buildings along a cross section of town. In addition to the psychiatric wards at the county hospital, for instance, the San Francisco County Short-Doyle program maintains contracts with nine distinct community agencies, and during fiscal year 1966-67 channeled 3,130 patients through these private resources.

Federal legislation originally passed by Congress in 1963 provided for the construction and staffing of community mental health centers, thus giving further impetus to the expansion and diffusion of mental health services in metropolitan communities. Several modern community mental health centers have been constructed with state, federal and local funds and then staffed and administered by the local Short-Doyle program. Santa Clara County alone has dedicated three new mental health centers in very recent years.

Sparsely populated rural counties, of course, experience entirely different problems from those of large metropolitan areas, and the rural Short-Doyle program tends to show a somewhat different complexion. Low tax bases, remoteness and lack of professional mental health personnel resident in the community have forced considerable ingenuity in establishing practical and efficient programs that fully meet the population's needs. Many of these rural Short-Doyle programs have contracted with neighboring counties for part-time services, or for the services of travelling clinical teams.

The reader may wonder whether counties and cities are able to develop local mental health services without also establishing a Short-Doyle program. Strictly speaking, it is entirely possible, but practically speaking the financial provisions of the Short-Doyle Act have, in effect, all but assured that local mental health services in California would develop through the state-county Short-Doyle plan. There is little incentive for a county

TABLE. 1.—*Growth of the Short-Doyle Program*

<i>Short-Doyle Appropriations</i>	<i>Admissions of Patients to Short-Doyle Programs</i>			
	<i>Fiscal Year</i>	<i>Inpatient Services</i>	<i>Outpatient Services</i>	<i>Rehabilitation Services</i>
\$ 3,130,500	1961-62	7,445	15,459	1,301
3,225,000	1962-63	9,763	22,848	1,643
5,450,000	1963-64	22,562	32,869	2,823
11,679,948	1964-65	37,224	49,355	2,884
14,811,727	1965-66	39,681	71,050	4,371
18,600,733	1966-67	41,601	81,294	6,292
24,801,030	1967-68	42,053	93,888	8,585

to undertake the full expense of a local mental health program if it can receive reimbursement for 75 percent of the cost. While there are occasional incidents where small citizen groups express distrust of state involvement in local affairs, the Short-Doyle program in California has not generally proved unpalatable to counties, for there are many liberal provisions for local option and control.

Growth of Community Mental Health Services in California

Local public mental health services grew very rapidly after the passage of the Short-Doyle Act. During the first fiscal year following its adoption seven local governing bodies made application and received reimbursement for community mental health programs established in accordance with the Short-Doyle Act. These programs became known as Short-Doyle programs, and each of them provided at least two of the five services described earlier. Table 1 shows how rapidly community mental health services have developed in California, both in dollars invested and in the number of patients reached through the community approach.

The total Short-Doyle program in the State of California, all county and city members considered, has grown with particular swiftness in the last five or six years. In 1962, for example, there were 20 Short-Doyle programs. Five years later there were 40. All but three counties with a population over 50,000 have established Short-Doyle services; and even some sparsely populated northern counties not technically considered Short-Doyle providers have broken ground for the development of local mental health services in the very near future, primarily through contractual agreements with adjacent counties or with travelling clinical teams.

All county Short-Doyle programs have developed outpatient treatment services. In addition, about 62 percent of existing Short-Doyle pro-

grams maintain inpatient services, frequently in wards of the local county hospital or in private hospitals through contractual agreements.

Implications of Change

The Short-Doyle Act was originally designed with the objective of establishing mental health services which would be available to the citizen near his home. At the signing of the Short-Doyle Act many progressive leaders in the mental health field considered the ideal course of treatment for a mentally ill patient to be similar to that for any person who had a medical problem. If the nature of the patient's disease is such that he can be successfully treated through prescription drugs and a schedule of outpatient visits to the physician or clinic, it would generally be inappropriate to insist that he be put into a hospital. Only if the disease or difficulty becomes critical or reaches a point where admittance to a hospital is strongly indicated, need the patient prepare for reception in a hospital ward.

Leaving that relatively small group of patients who are dangerous out of consideration, why should treatment for an individual whose illness is primarily "mental" be different from treatment for patients with other medical problems? For practical reasons, however, so long as the only public supported psychiatric inpatient services were located in state hospitals, treatment near home was not always feasible, especially for the patient unable to pay.

It can be fairly stated that the rise of mental health services at the community level has played the most important role in opening the door to psychiatric hospitalization near home. Other factors have entered the picture, such as the advent of Medi-Cal and the liberalization of certain hospital insurance plans, but these developments in relation to the Short-Doyle program have acted as sources of encouragement, facilitating the flow of patients into the system itself.

The effect of the growth of Short-Doyle programs on state hospital population figures is not entirely clear. Correlational studies*, however, would seem to indicate that the emergence of community services, particularly inpatient services, has had a definite bearing on the reduction of first admissions to state hospitals.

*Ferdun, Gareth, On the Impact of Short-Doyle, California Data, 1(2):54-75, Aug.-Sept. 1967.

Recent Developments

The rapid development of local mental health programs and the change in patterns of hospitalization naturally led to further intensive studies of public mental health services and to revisions in the law affecting the statewide Short Doyle program.

The California Mental Health Act of 1967 was the direct result of a two-year legislative interim study on the commitment procedures for mentally disordered patients to California state hospitals. The first part of the act, known as the Lanterman-Petris-Short Act, revised California commitment laws and provided a new course for the involuntary care and treatment of certain classes of mentally disordered patients*. The second part, which is of specific interest to us here, revised the old Short-Doyle Act in a number of significant ways. This part which we may refer to as the Revised Short-Doyle Act was further refined by legislative action during 1968.

The new Short-Doyle Act will not be completely implemented until 1 July 1969, but its salient features can be summarized as follows:

1. Each county with a population over 100,000 is required to establish a community mental health program to cover the entire area of the county. The present law is permissive and allows the county to develop a Short-Doyle program at will.

2. The Short-Doyle mechanism will still remain the instrument by which a county may receive state aid for the development of community mental health services. The reimbursement formula is changed, however, from 75 percent-25 percent to 90 percent-10 percent, the state share being 90 percent and the county share 10 percent. While county Short-Doyle programs will be reimbursed a greater amount of money by the state, they must purchase state hospital care for mentally ill residents of the county (except the judicially committed) with these funds.

3. Local Short-Doyle programs and state hospital services to mentally disordered county patients will therefore be coordinated into a single system of care. The county Short-Doyle program will be responsible for the provision of all public mental health services to residents of the county, utilizing county facilities when feasible and con-

*Editor's note: See page 403 for Brickman, H. R.: California's Short-Doyle Program: The New Mental Health System—Changes in Procedure; Implications for Family Physicians, Calif. Med., 109:403-408, Nov. 1968.

tracting with nearby state hospitals for services when necessary.

4. In order to provide a basis for reimbursement and to avoid duplication and fragmentation of effort, the law will require every county to develop a plan outlining the services it wishes to establish on a priority basis. This county Short-Doyle plan must receive the approval of the Department of Mental Hygiene before the state will reimburse the county 90 percent of the cost of community mental health care. It is intended that the county plan include the fullest possible participation of all existing private and public resources within the county.

5. The number and kind of mental health and mental health related services that a county Short-Doyle program may include and for which it may receive 90 percent reimbursement from the state will be expanded from the present five to ten. These services are:

1. Inpatient services;
2. Outpatient services;
3. Partial hospitalization services, such as day care, night care, weekend care;
4. Emergency services 24 hours per day available within one of the three services listed above;
5. Consultation and education services available to community agencies and professional personnel and information services to the general public;

6. Diagnostic services;

7. Rehabilitative services, including vocational and educational programs.

8. Pre-care and after-care services in the community, including foster home placement, home visiting and half-way houses;

9. Training;

10. Research and evaluation.

A quick comparison of these ten new services with the five services outlined in the original Short-Doyle Act will show that a more comprehensive program and a greater variety of treatment measures will soon be possible. Inpatient psychiatric treatment, for instance, is no longer restricted to the setting of a general hospital or a psychiatric hospital affiliated with a general hospital. It is hoped that local mental health programs will be able to utilize this new flexibility in the fuller development of psychiatric treatment patterns, particularly the provision of immediate crisis intervention.

As indicated earlier, public mental health services, particularly at the county level, have experienced a remarkable growth in the last ten years. The California Mental Health Act of 1967, as revised in the 1968 legislative session, can be reasonably expected to create further impetus to the development of these programs, with many far-reaching implications.

California's Short-Doyle Program

The New Mental Health System

Changes in Procedure • Implications for Family Physicians

HARRY R. BRICKMAN, M.D., *Los Angeles*

FOR MANY YEARS California has been a leading state in the improvement of existing public mental health facilities and in the development of new programs to meet the needs of its rapidly increasing population. Physicians, other professionals, interested citizens and legislators have worked together to improve the state hospital system, and to establish community prevention and treatment services under the Short-Doyle Act. The most recent culmination of these years of effort took place with the passage and signing by the Governor of A.B. 1454 and A.B. 1950 which, together with two legislative acts passed in the 1967 California legislature, will in effect revolutionize the entire system of public mental health care in the state, beginning 1 July 1969. This legislation drastically changes the conditions under which persons may be treated involuntarily for mental illness,* and also provides for the establishment of a single system of public mental health care administered by units of local government under the general supervision of the California Department of Mental Hygiene.

Under the old provisions of the Welfare and Institutions Code, persons requiring involuntary psychiatric care were processed for the most part by Superior Courts and committed for indefinite periods to state hospitals for care and treatment. At the same time they incurred severe civil disabilities such as automatic loss of driver's license, inability to engage in various businesses and profes-

sions, and loss of the right to vote (after six months).

The indications for commitment for mental illness were changed through the passage of A.B. 288 during the 1967 legislative session. This bill permitted judicial commitment of only those persons dangerous to themselves or others as well as in need of supervision, treatment, care, or restraint by virtue of mental illness. It abolished judicial commitment for persons who are not dangerous. It also required a written statement by a physician that the person is dangerous to himself or to the person or property of others before a petition requesting judicial examination of the person could be made or filed. This provision became effective 8 November 1967.

Public community psychiatric facilities were first established as outpatient clinics of the State Department of Mental Hygiene beginning in 1946, but the greatest increase in local mental health programs occurred as the result of the passage of the Short-Doyle Act by the California legislature in 1957. This Act permitted local communities to develop their own programs of mental health prevention and treatment, with state general supervision and funding subvention, the latter ranging from 50 percent to 75 percent of total program cost. The Short-Doyle program in California expanded considerably so that a total of 41 local programs were operative in the state by 1967, with a volume of patient services which substantially exceeded those provided by state hospitals. Many patients who otherwise would have been committed to state hospitals were being treated in local

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*Exceptions are made in the case of mentally disordered criminal offenders and sex offenders, the mentally retarded and other groups characteristically under state care.

Short-Doyle programs although a substantial number of patients were still being committed to state hospitals, largely because of inadequate local treatment facilities.

Under the mental health centers construction and staffing legislation passed by Congress in 1963, 1964 and 1965, a number of new federally funded facilities were established in California for local prevention and treatment of mental illness. Many of these facilities were connected to local Short-Doyle programs or anticipated contractual relationships in the future.

With the encouraging growth of the Short-Doyle program it was felt that further legislative steps were necessary to encourage a more rapid transition of primary responsibility for mental health care from the old state hospital system to the new system of community mental health programs.

The New Mental Health Legislation

Senate Bill 677, passed in the 1967 legislative session, and Assembly Bills 1454 and 1950 in the 1968 session are incorporated in a new Division 5 of the Welfare and Institutions Code. Part I of this Division is known as the California Mental Health Act, or the Lanterman-Petris-Short Act, named after the legislative sponsors. Part I ends indefinite involuntary commitment, eliminates automatic civil disabilities, and provides for a system of prompt evaluation and treatment of seriously mentally disordered and chronically alcoholic persons. (See accompanying chart for system of providing involuntary care.) Extensive provisions for judicial review are built into the legislation. Part II is an extensively amended Short-Doyle Act providing for the fiscal and administrative implementation of Part I, and for the continuation of the Short-Doyle Program.*

Provisions for Involuntary Treatment

The aims of the Lanterman-Petris-Short Act of 1967 are best communicated through a direct quote of Section 5001:

"5001. The provisions of this part shall be construed to promote the legislative intent as follows:

"(a) To end the inappropriate, indefinite, and involuntary commitment of mentally disordered persons and persons impaired by

chronic alcoholism, and to eliminate legal disabilities;

"(b) To provide prompt evaluation and treatment of persons with serious mental disorders or impaired by chronic alcoholism;

"(c) To guarantee and protect public safety;

"(d) To safeguard individual rights through judicial review;

"(e) To provide individualized treatment, supervision, and placement services by a conservatorship program for gravely disabled persons;

"(f) To encourage the full use of all existing agencies, professional personnel and public funds to accomplish these objectives and to prevent duplication of services and unnecessary expenditures."

Persons for whom evaluation and treatment for serious mental illness is needed will receive these services at facilities designated by the counties to provide 72-hour treatment and evaluation services. These are not intended by the legislation as merely psychiatric "holding operations," but rather to provide necessary treatment services to the patients. Patients are accepted by these facilities either by written application by a peace officer or professional person, or by court order initiated by any person, and subject to pre-petition screening before actual issuance by a Superior Court judge.

The Act also provides for 14-day intensive treatment upon certification by the professional staff of a 72-hour facility that the person is, as a result of mental disorder or impairment by chronic alcoholism, a danger to others or himself, or is gravely disabled, and provided also that the person has been advised of but has not accepted voluntary treatment. A court order is not required for this certification but it is subject to judicial review under habeas corpus proceedings in a Superior Court. For suicidal persons the 14-day intensive treatment certification may be renewed for an additional 14 days.

There is a provision in this Act for a 90-day treatment period for those who after a period of 14-day intensive treatment are, as a result of mental disorder or impairment by chronic alcoholism, presenting an imminent threat of substantial harm to others. This period of treatment is initiated by the professional person in charge of a 14-day intensive treatment facility through a petition to the Superior Court. The period is not to exceed

*See Beach, W. B., Jr., and Davis, A.: Short-Doyle Program—Past, present and future, (Government and Medicine), Calif. Med., 109: 398-402, Nov. 1968.

(Lanterman-Petris-Short Act)

Involuntary Care Provisions

72-HOUR TREATMENT AND EVALUATION

WITHOUT COURT ORDER

Any person who "is, as a result of mental disorder, a danger to others, or to himself, or gravely disabled."

Patient Description

Initiated by:

A peace officer or other professional person who takes patient into custody and places him in treatment facility. Written application is then made to facility by peace officer or professional person.

Location of Treatment

County designated and State approved facility. Evaluation and treatment can be performed without detention depending on professional judgment.

Term of detention or treatment

Not to exceed 72 hours, exclusive of Saturdays, Sundays and holidays.

Disposition

- Release.
- Referral for further care and treatment on voluntary basis.
- Certification for intensive treatment under 14-day procedure.
- Recommendation for conservatorship.

ON COURT ORDER

Any person alleged, as a result of mental disorder, to be a danger to others, or to himself, or to be gravely disabled, or a chronically alcoholic criminal defendant similarly qualified in counties with appropriate facilities.

Any person. Application is made to person or agency designated by county for petition requesting evaluation of patient. Person or agency designated by county to provide "pre-petition screening", determines whether there is probable cause to believe allegations. Screening shall also determine whether patient will agree voluntarily to receive professional counseling or evaluation. In cases of chronic alcoholism, initiated by Municipal Court judge.

If court order is refused, peace officer or court approved official may take into custody and place in designated facility for evaluation and treatment.

Not to exceed 72 hours, exclusive of Saturdays, Sundays and holidays.

- Release.
- Referral for further care and treatment on voluntary basis.
- Certification for intensive treatment under 14-day procedure.
- Recommendation for conservatorship.

14-DAY INTENSIVE TREATMENT BY MEDICAL CERTIFICATION

If patient has been detained for 72 hours under any of the 72-hour procedures and has received evaluation, he may be certified for intensive treatment if professional staff of agency or facility providing evaluation services has analyzed person's condition and has found person is, as a result of mental disorder or impairment by chronic alcoholism, a danger to others, or to himself, or gravely disabled, and person has been advised of, but has not accepted, voluntary treatment.

Notice of certification signed by professional in charge of agency or facility providing evaluation services (under 72-hour detention) and a physician, if possible a board qualified psychiatrist who participated in the evaluation. If professional person in charge is physician who performed medical evaluation, the second person to sign may be another physician, unless one is not available, in which case, a psychologist, social worker, or registered nurse who participated in evaluation should sign certification. No commitment order is involved.

County-designated facility equipped and staffed to provide intensive treatment.

Not to exceed 14 days (may be shorter); 14-day period may be renewed once if patient is suicidal.

- Release.
- Further treatment on voluntary basis.
- 90-day treatment for imminently dangerous.
- Conservatorship.
- Right to judicial review by writ of habeas corpus in superior court.

90-DAY POST-CERTIFICATION TREATMENT FOR IMMINENTLY DANGEROUS PERSONS BY COURT ORDER

At end of 14-day intensive treatment period, a person who has threatened, attempted, or actually inflicted physical harm upon the person of another and who, as a result of mental disorder or impairment by chronic alcoholism, presents an imminent threat of substantial harm to others.

Professional person in charge of 14-day intensive treatment facility, or his designee, by a petition to superior court. Petition may be filed with the superior court at any time after first week of 14-day intensive treatment period.

If court finds person to be in need of 90-day treatment, it shall remand him to the Department of Mental Hygiene or court designated facility for that purpose.

Not to exceed 90 days (may be shorter).

- Release at end of 90 days, or before.
- If superintendent or professional person in charge of hospital in which patient is confined files with superior court a new petition on grounds that he has threatened, attempted, or actually inflicted physical harm to another during his 90-day detention and treatment and that he is a person who, by reason of mental disorder or impairment by chronic alcoholism, presents an imminent threat of substantial harm to others, court procedure would start over again and if court so orders at end of court hearing, patient would be detained for additional 90-day period.
- If superintendent or professional person in charge of hospital providing 90-day treatment releases patient before end of 90-day period, he must notify court which remanded patient for treatment.

CONSERVATORSHIP FOR GRAVELY DISABLED

Any person who is gravely disabled as a result of mental disorder or impairment by chronic alcoholism.

Recommendation of professional person in charge of agency providing 72-hour evaluation or 14-day treatment. If court designated officer recommends conservatorship, petition is filed in Superior Court.

Patient may be placed by conservator in a medical, psychiatric, nursing or other state-licensed facility, or a state hospital, county hospital, hospital operated by Regents of the University of California, or United States Government hospital; or in addition to any of the foregoing, in cases of chronic alcoholism, to a county alcoholic center.

Conservators may be appointed by court for successive periods of one year. Petition to court for renewal of conservatorship must include opinion of two physicians that conservatee is still gravely disabled. At any time, but not to exceed more than once each six months, conservatee may petition superior court for a rehearing as to his status.

Discharge from conservatorship or continuation on yearly basis by court.

90 days but it may be renewed for an additional 90 days if the person concerned threatened, attempted or actually inflicted physical harm to another during the first 90 days. Finally, the Act provides for the appointment by the court of conservators for people who are gravely disabled as a result of mental disorder or impairment by chronic alcoholism. Under the court conservatorship, the patient may be placed by the conservator in any one of a variety of facilities. Conservators are appointed by the court for only one year at a time, but this is renewable upon petition to the court, with the concurrence of two physicians. The provisions which prescribe evaluation and treatment services for chronic alcoholics are optional with counties, who may elect to establish facilities for the care of this group of patients.

Part II—Changes in the Short-Doyle Act

The Act establishes a single system of mental health care and of public appropriation for mental health care in California. In its major features it:

- Creates a single appropriation for mental health services in the State budget integrating the state hospital and the Short-Doyle system. State funds will be allocated in accordance with the priority needs in approved County Short-Doyle Plans.
- Establishes a new formula (90 percent State, 10 percent County) for financing all public mental health services, regardless of where services are provided. This eliminates any financial incentive for serving patients in state-operated rather than local facilities.
- Establishes a system of priorities for the expenditure of mental health funds. This system accords first priority to provision of required services for involuntary patients under Part I of the new Mental Health Act and for diagnostic screening of voluntary patients admitted to state hospitals. Second priority is allotted to the maintenance of existing Short-Doyle services and to care of state hospital patients admitted before 1 July 1969. Third priority is assigned, within the limit of available funds, to funds for the expansion of existing programs, for provision of services to voluntary patients entering state hospitals after 1 July 1969, or for the establishment of new Short-Doyle programs.
- Requires counties, as a precondition for receiving State funds, to prepare a County Short-Doyle Plan to make maximum use of all resources

and avoid duplication and unnecessary expenditures. State hospital services are to be included in such plans.

- Delays the operative date of the Lanterman-Petris-Short Act to 1 July 1969, to coincide with the new (90 percent-100 percent) financing for all services.

- Permits counties with small populations (under 100,000) the option to participate in the new mental health system. If declining to participate, such counties may elect the provision of voluntary care and involuntary services in state hospitals for their residents with the cost of such care, except to the extent patients are able to pay, borne entirely by the State.

- Limits any possible increased cost to any county (1 cent per \$100 assessed valuation) in any one fiscal year.

- Provides that the State will maintain its effort in mental health and that all programs will operate within the limits of funds appropriated.

- Guarantees, through a "grandfather" clause that there will be no cutback in existing Short-Doyle programs.

- Requires the Department of Mental Hygiene to prepare a statewide plan for the orderly and economical development of mental health services.

- Does not alter existing mental health caseload, but sets up a more equitable structure for the distribution of funds for mental health services.

- Increases the size and composition of the local mental health advisory board to a total of 13 members, of whom a minimum of three shall be physicians.

- Establishes a citizens' advisory council to assist the State Director of Mental Hygiene in administration of the new mental health system. The council is to be composed of 15 appointed voting members, of whom a minimum of four shall be physicians.

- Requires that the State Department of Mental Hygiene establish by 1 October 1970 a five-year state plan for community mental health services, and that the Department submit to the legislature not later than 1 January 1969 a statement of goals to be achieved in California's mental health system, and proposals as to how the system can be evaluated to determine the relative effectiveness of the various services in accomplishing the desired goals.

Discussion

The positive humanitarian effects of this new mental health legislation are undeniable. The civil liberties of individuals who are dangerous to themselves or others, or gravely disabled by virtue of mental disorder, are guaranteed through a variety of provisions.

The new legislation imposes a number of safeguards against involuntary treatment of persons who do not meet the established criteria. At each legal step in the process of providing involuntary treatment, patients are to be informed of their rights to judicial review under the doctrine of habeas corpus, and the meaning of the procedure is to be explained. Specific acts of "dangerous behavior" are to be described by their physicians, and patients are to be informed of these allegations.

The new legislation implements a widely held philosophical conviction that society should restrict a citizen's freedom only if he is a clear threat to the welfare and safety of himself or others. This tends to conflict with some of the humanitarian views of psychiatrists and other professionals who hold that, if medical judgment determines that mental illness has paralyzed the ability of a person to recognize his own mental illness and to request needed treatment, a suitable protective provision should be written into the law to allow for involuntary treatment quite apart from the issue of dangerousness.

A further implication of the heavy emphasis in this legislation on civil guarantees is that it can place physicians in an adversary role in regard to their patients and require the spending of a physician's time in courts as a party to an action for involuntary treatment. It has been held that the adversary role is incompatible with the physician role. Having succeeded in recommending incarceration by testifying that a patient is dangerous, the physician may be in a poor position to ask the same patient to reveal his innermost thoughts and feelings to his adversary of yesterday.

With regard to the fiscal provisions of the law, the 90 percent-10 percent division between state and local financing seems more equitable than the old method in view of local governments' relatively limited tax resources. The establishment of a vastly expanded system of local mental health facilities for both involuntary and voluntary mental health care in the public sector, however, will require substantial increases in funding. It is difficult to forecast a rapid change in mental health programs

if new local programs can be established only at the expense of immediately diminishing state hospital admissions and thereby diverting those funds to the new local programs.

Implications for the Family Physician

With the abolition of the old court commitment system and of the Health Officer application, the family physician, in the case of a patient who is unable to afford private care, and who is unwilling to accept psychiatric care voluntarily, will be obliged (after 1 July, 1969) to refer him to a county Short-Doyle facility in either of two ways: First, he may seek 72-hour treatment and evaluation without a court order by actually taking the patient to the treatment facility or having him taken there by some other interested person. The person taking the patient to the 72-hour facility will be required to submit an application in writing stating the circumstances under which the patient's condition was called to his attention and stating his belief that from his personal observations, he believes that the patient, because of mental disorder, is a danger to himself or others or gravely disabled by mental disorder to the extent of being unable to provide for his basic needs for food, clothing or shelter. If, in the judgment of the professional person in charge of the facility providing evaluation and treatment, or his designee, the patient can be properly served without being detained, he will be provided evaluation, crisis intervention, or other inpatient or outpatient services on a voluntary basis. Second, if the family physician is unable to take the patient to a treatment facility or to arrange for his transportation there, he may make an application to the person or agency designated by the county for a court petition requesting evaluation of the patient. The person or agency processing the petition will provide pre-petition screening to determine whether there is probable cause to believe the allegations. The screening will also determine whether the person will agree voluntarily to receive professional counseling services or an evaluation in his own home or in a facility designated by the county.

Following pre-petition screening, the petition-processing agent will file the petition if satisfied that there is probable cause to believe that the person is, as a result of mental disorder, a danger to others or himself or is gravely disabled, and the patient will not voluntarily receive evaluation or professional counseling. If, after a petition is filed,

the patient refuses or fails to appear for evaluation at the time and place set forth in a court order, a peace officer or other court-appointed official shall take him into custody and place him in a facility designated by the county.

As a safeguard against malicious or unprincipled action under the provision for petition, the law provides that any person who seeks a petition for court-ordered evaluation although knowing that the person for whom the petition is sought is not, as a result of mental disorder, a danger to himself or others or gravely disabled, is guilty of a misdemeanor or may be held liable in civil damages by the person against whom a petition was sought (Section 5203).

Under the new legislation there will be only two methods of entry into the public system for involuntary mental health care. Local physicians, as well as other professionals in the community, can anticipate that many patients referred for public mental health care under this system will be

returned to their homes after relatively short periods. It is important to emphasize that the mere presence of even severe mental illness which is not characterized by dangerousness to self or others or by grave disablement as defined by this legislation will *not* be a sufficient criterion for involuntary public mental health care. Anticipating the likelihood that an increased number of persons with mental illness will be remaining in the community, it is obvious that, in addition to the expansion of voluntary outpatient and inpatient psychiatric facilities, the services of non-psychiatric physicians will be increasingly needed to assist in treatment efforts in the community. There will undoubtedly be an increasing call by local mental health agencies for professional collaboration with physicians in the community, with the hope that the family physician will be willing and able to provide office treatment with psychopharmacological agents, supportive psychotherapy and other measures which can be successful in maintaining patients with psychiatric illnesses in their community.

University of California, San Diego

IN DECEMBER 1959, a committee appointed by President Clark Kerr of the University of California reported that the establishment of a new medical school in or near San Diego was feasible and that community cooperation was assured. Those responsible for rebuilding the San Diego County General Hospital invited the Regents of the University to participate in planning the new hospital with a view toward its playing a major role in the proposed new medical school. In October 1962, the Regents decided that preclinical facilities and a University Hospital would be located on the newly developing La Jolla Campus of the University of California, San Diego, and that a significant portion of clinical instruction should take place at the county hospital. Subsequently, the Veterans Administration began to plan for a new hospital to be developed as an integral part of the La Jolla medical campus complex.

In July 1966, full operation of the county hospital was assumed by the University through an operating agreement with the County of San Diego, and the hospital is now officially designated as "University Hospital of San Diego County."

Meanwhile, in September of 1966, ground was broken for the first building for the school. It was scheduled for completion late in 1968. The building was designed to house the basic sciences facilities, the biomedical library and the administrative offices. Present plans call for the completion of a second building in early 1971 to house the clinical sciences facilities, and of a Veterans Administration hospital later the same year. The Campus Clinical Center should be ready in 1973-74. Thus the physical core of the School of Medicine is being established close to the new facilities of Revelle, John Muir and other UCSD colleges.

Organization

The new School of Medicine and the general campus of the University are developing simultaneously, thereby providing unique opportunities for integration of the teaching and research of the two. The medical school academic master plan provides for assignment of some faculty positions to general campus departments for persons whose scientific interests relate to medicine and human biology. The faculty members occupy space in the School of Medicine, accept teaching responsibility within the medical curriculum, and create special courses or contribute to interdisciplinary teaching to emphasize aspects of their discipline most useful to medical students.

Nine medical school departments are being developed: Community Medicine, Medicine, Neurosciences (which includes a Division of Clinical Neurology), Obstetrics-Gynecology, Pathology, Pediatrics, Psychiatry, Radiology, and Surgery. Each of these departments has teaching responsibilities which extend over the four medical school years and through postgraduate training. An internship and residency training program is now under way at University Hospital.

The School of Medicine is surrounded by abundant learning resources representing all disciplines of a general university campus. Extensive interactions are being fostered between teaching and research activities of medical school departments and undergraduate and graduate programs of the general campus. Additional sources of strength are the San Diego County Medical Society, the Salk Institute for Biological Studies, the Scripps Clinic and Research Foundation, the Western Behavioral Sciences Institute, and the research programs of the San Diego Zoo. The University's Scripps Institution of Oceanography (SIO) is especially important. Among ships sent to all parts

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of the world is Research Vessel *Alpha Helix*, designed expressly for the conduct of biomedical research in locations where challenging physiological problems of human, animal and plant life can best be studied.

The Basic Science Building, the Clinical Science Building, the Campus Clinical Center and the Veterans Administration Hospital will make up a closely integrated complex on the La Jolla campus. The Basic Science Building will house faculty of campus participating departments and certain divisions of medical school departments. The medical school departments will be located chiefly in the Clinical Science Building and in the hospitals. The Biomedical Library, included within the initial basic science construction project, will serve the faculty of the entire UCSD campus and the School of Medicine. The projected size for fall 1968 is 60,000 volumes and more than 3,000 periodicals.

Three hospitals will be utilized by the medical school. The University Hospital of San Diego County, located 13 miles south of the main campus, will provide students with a broad spectrum of health care problems. The UCSD Clinical Center in La Jolla will provide a patient group selected for research and teaching interest, and the Veterans Administration Hospital will further extend the range of clinical facilities for the school.

The Office of Learning Resources (OLR) of the UCSD School of Medicine has responsibility for effective teaching, including the devising and introduction of newer methods. Unlike the library, which is concerned with handling of knowledge in book or journal form, OLR produces, gathers, disseminates and stores non-printed informational materials. Components for presenting tactile, auditory and visual information are catalogued and available to faculty and students.

OLR also administers instructional areas of the medical school. As lecture halls and laboratories are to be electronically equipped and interconnected with computer facilities, it will be possible to introduce innovations and evaluative research in computer-based instruction and other techniques for more effective learning.

Curriculum

The main objective of the school's curriculum is to develop critical, objective and humane physicians who are equipped for changing conditions and continuing self-education. Each student is expected to acquire an understanding of basic medi-

cal sciences adequate to appreciate and utilize the vast new scientific resources available to modern medicine. Beyond this, students will be encouraged to concentrate on special areas of interest leading toward their special role in a diversified medical community. Each student will have access to the best facilities and counseling to exercise and strengthen his individual capabilities.

Curricular form and content, therefore, are to be adapted to the particular needs of each student. Advisers will examine each student's interests at entrance, help to refine his developing interests during the medical school years and provide a critical examination of alternative career objectives. The adviser will explore with the student the requisite courses of study, the best locales for these studies, and the influence of probable future social developments on his career objectives. A small-group tutorial system will be maintained throughout the four-year curriculum, designed specifically to encourage these explorations and definitions.

The curriculum is divided into two major parts: The core curriculum, and the elective programs. The core curriculum embodies those aspects of medical education deemed essential to every medical student regardless of background or ultimate career direction. It includes courses in biomathematics; cell biology and biochemistry; organ physiology and pharmacology; basic neurology; pathology and microbiology; gross anatomy, social and behavioral sciences; an introduction to clinical medicine in the first two years; clinical clerkships in the third year; and primarily elective training in the fourth year. At faculty option, students with advanced training in a core area may take additional advanced work in this or another area, may utilize available time to overcome deficits in preparation, or begin independent study.

Instruction in clinical medicine will begin early, with students being introduced to patients with diseases that illustrate subjects covered in the basic science courses. Students also begin to acquire the necessary clinical techniques during "Introduction to Clinical Medicine." Training in differential diagnosis and clinical medicine is condensed into the third year.

Core courses in clinical medicine include the major clinical specialties taught in hospital settings and out-patient situations, and may include extended care programs. A specific selection of subspecialties is determined by the student after consultation with his faculty advisers. Strong emphasis is

placed on methods for collating information to be used in clinical problem-solving.

Students also study the roles of medicine and physicians in society. Relevant course material is presented by medical school faculty, by instructors from other segments of the university, and by invited speakers.

The elective programs offer each student a set of choices suited to his unique background, ability and career objectives. Each student is expected to select a "Concentration Area" which combines those didactic and research experiences at UCSD or elsewhere which best suit his needs.

Purposes of the elective programs are to encourage and assist students to achieve their individual objectives as members of the medical profession; to provide concentrated preliminary training for careers in subdivisions of the medical profession, including academic research and teaching, health systems planning, public health, international medicine, or one of the many clinical specialties; to effect a match between career orientation, diversity of background and previous training.

The curriculum provides substantial elective opportunities, including experience in the process of investigation. Elective programs occupy approximately one-fourth of the total time in the first two years and two of the three quarters in the fourth year. Students are also expected to utilize at least two of the three summers toward completion of their elective major. The School of Medicine makes every effort to assist in placing students and obtaining financial support for summer work related to elective Concentration Areas. Work may be accomplished within the School of Medicine, on the general UCSD campus, or off-campus — wherever it may be done most effectively. A faculty committee on electives supervises individual programs.

Concentration Areas are conceived to be broad but definable topics relevant to career objectives. In some ways, the concept resembles a "major" in college but is considerably more flexible. A Concentration Area may include a number of formal courses or very little course work, and may commence in the first or second year. There may be emphasis on investigative experience first in apprenticeship and, ultimately, independent research. Work in a Concentration Area is expected to culminate in a written report ordinarily expected by the end of the fourth year as a requirement for graduation. This dissertation may be based upon

laboratory or clinical investigation. It will be judged for scientific and scholarly merit, will be formally reviewed, and may be submitted for publication. Among the Concentration Areas at present under development, the following may be identified: Marine and Aerospace Biomedicine, the Neurosciences, Bioengineering for Medical Students, Developmental Biology, Health Systems and Administration, Microbiology and Infectious Diseases, Immunobiology and Transplantation, Genetics (including molecular and Medical Genetics), Experimental Surgery, Pathobiology, Cardiovascular Medicine, and Endocrinology and Metabolism. Additional programs, including particularly the clinical specialties, are also being developed.

UCSD School of Medicine plans to utilize comprehensive end-of-year examinations, graded only "pass" or "fail." The National Board Examinations will be required and should provide some external evaluation of the new programs.

The Charter Class

A Charter Class of outstanding students entered UCSD's School of Medicine in September, 1968. The 48 entrants were selected from well over a thousand applicants on the basis of scholastic ability, recommendations by their teachers, and at least three interviews with UCSD faculty members. The students are coming from 13 California colleges and 15 colleges outside California.

As undergraduates, members of the Charter Class accumulated a mean grade point average of 3.4 on a 4 point scale. The cumulative mean Medical College Admissions Test score was greater than the 80th percentile.

Several in the Charter Class have published the results of original work, and others have taken advanced training at one or another of the nation's scientific research institutions — Argonne National Laboratory, Scripps Institution of Oceanography, the Hopkins Marine Station, Woods Hole, and graduate departments in several universities. In addition to their scientific achievements, these young people show a striking assortment of talents and interests, especially in music, with well over half the class having advanced competence on a musical instrument.

Faculty

Under the leadership of Clifford Grobstein, Dean of the School of Medicine and Vice Chancellor for Medicine and the Biological Sciences, the

faculty of the UCSD School of Medicine has been expanded rapidly. At present, the full-time faculty in the participating and medical school departments numbers 70. Department chairmen have been appointed in the departments of Community Medicine, Medicine, Neurosciences, Pathology, Pediatrics, Radiology, and Surgery. Appointments in Psychiatry, and Obstetrics/Gynecology are expected shortly.

In addition to the full-time members, 16 dis-

tinguished scientists have joined the faculty as professors in residence. For the most part, they occupy positions at renowned institutions in the San Diego area. In numbers, the faculty has doubled in the past year and shortly will double again.

The combination of an outstanding faculty, magnificent facilities and an able and highly selected charter class augurs well for the launching of this newest of California's medical schools.

CLIFFORD GROBSTEIN, PH.D., Dean

CHOOSING THE SITE FOR BREAST BIOPSY

"I think it's always a good idea when you do an excisional biopsy [of the breast] to place it so that it's easiest to do a radical [mastectomy] after you've done the biopsy, even though you think it's a fibroadenoma or something similar. You can really put yourself into a difficult situation if you don't think ahead to the possibility of finding a carcinoma. So that ordinarily we try to make our biopsy central in the breast, central to the lesion—in other words, between the lesion and the nipple—so that we can get around that area with an en bloc excision later more practically."

—JEROME A. URBAN, M.D., New York City
Audio-Digest Surgery, Vol. 15, No. 17



The Scope and Responsibility of Medicine

A Forum with a Purpose

To engender discussion of what the scope and responsibility of medicine ought to be in today's society, CALIFORNIA MEDICINE printed in its June issue six essays by authors known to have keen if various interest in the subject.

In presenting the essays the editors expressed hope that they would be the beginning of a forum from which a definition of our profession's responsibilities may be distilled. Readers were invited to take part in a continuation of the forum in succeeding issues. Following are three contributions selected from those received to date. Others will be published in the months ahead.

If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California 94102. Keep your essays short, please.

PHILIP R. LEE, M.D.

Washington, D.C.

*Assistant Secretary for Health and Scientific Affairs,
U.S. Department of Health, Education, and Welfare*

IN LOOKING AT this challenging and very perplexing subject, I think it is important to keep two things in mind: The scope of medicine and the demands placed upon it are constantly changing. The responsibility of medicine is not.

It seems to me that the problems and conflicts we in the medical profession are facing fundamentally stem from this duality of tremendous change in the scope of medical science and technology and the problems it seeks to solve, balanced against what I think we all agree is the unchanging ethic of the healing arts.

No matter in what terms we express it, the responsibility of medicine always has been and always will be to prevent, cure, or ease the burden of illness. The steady and sometimes spectacular advance in the ability of medical science to meet this responsibility in no way alters the responsibility itself. Neither do the progressive changes in social conscience which now proclaim the right of every individual to health services of high quality. Indeed, health has become an essential part of both personal and national aspirations. Fundamentally this is

nothing more than the ethics of medicine striving for their highest level of expression.

The great emphasis in this country on the delivery of health services within the last decade is a forceful manifestation of the shift in the scope of medicine and the constancy of its responsibility. The fact that millions of Americans have not benefited from the great advances of medical science is the single greatest health challenge of our age, precisely because it is the responsibility of medicine to see that all the people do benefit.

Those of us in private practice, in education, in research, and in health administration are struggling with issues and problems that were scarcely recognized two decades ago, though they surely existed then. In essence those issues and problems resolve into one question: How can we broaden the scope of medicine to meet new health challenges without narrowing medicine's responsibility to serve all the people?

Efforts to develop new kinds of health manpower, to increase the productivity of health professionals, to design and erect better and more accessible health facilities, to narrow the time lag between research accomplishment and application, to curb the rise of health care costs, to lower economic, racial, geographic and other barriers to decent health care—each of these efforts is an attempt to reconcile the scope and responsibility of medicine.

From my point of view, both as a physician and as a public official, there is much that the health professions have to be proud of. Medicine today is able to deal with health problems that were frankly hopeless when I graduated from medical school twenty years ago. Yet we have failed and are failing to render vital services to the poor, to infants and children, to racial minorities, to rural Americans, to migrant workers.

Medicine and the means of delivering health care must be judged on the ability to fulfill their fundamental responsibility, which is to safeguard the health of people. People cannot refuse to be sick. They cannot decide when they will need medical attention or what kind they will need. Nor can people be sure that they will have access to adequate health care when they need it, not unless the medical professions and the health institutions, public and private, make certain that the scope of their efforts is as broad as their responsibility.

Thus it seems to me that the medical profession is being called on to develop a new sense of its responsibility, one that recognizes and draws upon the tremendous social, ideological and technological changes occurring in our society. The social ferment characterized and motivated by the quest for equality, the ideological revolution which dares to maintain that health care is a right and not a privilege, and the technological revolution which is producing the skills and resources that can permit society to achieve its goals—all of these forms of change demand corresponding changes in the scope of medicine.

It is our task not merely to react, but to guide, not merely to concede that medicine and the delivery of health services are being challenged as never before to meet the needs of society, but to accept this challenge as an opportunity to correct the imbalances and remedy the defects in the scope of medicine.

The success with which we rise to this challenge will determine the extent to which medicine can bring its ever broadening scope into line with its unchanged and unchanging responsibility.

JOHN R. GAMBLE, M.D.

San Francisco

A CONSIDERATION of the scope and responsibility of medicine implies a look into the future. The first step in such a consideration is to look backward at medical traditions to determine what is of value as a foundation for the future. If traditional medicine is to influence the future development of medicine, it is necessary to test the validity of the premises upon which its traditions are based. Those that have outlived their usefulness must give way to the reality of today.

Analysis of the traditional doctor-patient relationship is probably the most difficult to carry out with detachment. Whether or not the doctor's ego supports this concept, there is almost universal acceptance that it is good. It does, however, bear examination. There is little doubt that a large proportion of persons want treatment given in the most efficient manner with as little fuss as possible. Desire for economy and competence has superseded demand for personal service in medicine as it has in many other facets in contemporary living. Furthermore, most physicians agree that the team approach, where scientific knowledge can be utilized, provides superior patient care in any complicated illness.

On the other hand the art of medicine, which forms the basis for the doctor-patient relationship, becomes essential where science fails, particularly in the care of older persons whose infirmities resist scientific advances. There is inverse relationship between scientific advances and the art of medicine; as science has advanced the art

of medicine has diminished. The idea that health can be obtained, however, solely by the application of scientific standards has a faint 19th century aura about it suggesting a naive optimism tinged with arrogance. If man were a computer only, one might expect the art of medicine to die completely, but his humanness dictates the art of medicine must endure.

Research-oriented undergraduate and graduate education has resulted from the availability of large grants. Undoubtedly it has produced great advances in scientific knowledge. Whether the young physician product is best equipped to care for patients is a question that is being actively debated today; and there is an indication that, in the future, a greater proportion of medical school budgets will be used for experimentation with and study of efficient methods of delivery of medical services. The student most certainly will benefit from having trained in an atmosphere where a balance is maintained between emphasis on research and on patient care. Studies of these kinds must be done in a medical school environment and it is the responsibility of all physicians to promote them. Moreover, the medical students and young physicians today, more socially conscious than the older physician, are demanding a new approach to the delivery of medical services.

An additional responsibility of medicine—and one of its finest traditions—is to insure that the practicing physician will remain competent throughout his career. This tradition must be continued and receive even greater emphasis. Self assessment programs such as the one sponsored by the American College of Physicians have been a remarkable step in allowing the physician to judge his own competence.

It has been taught for many years that, given sufficient resources, disease can be completely prevented. Evidence accumulates which indicates that this is not true. For example, in British Columbia, where examination of cervical smears is done for almost every woman periodically, the death rate from carcinoma of the cervix has not changed appreciably. The study of the multiphasic screening program now under way at Kaiser Foundation Hospitals is an approach to determine what is good and what is not good. Results of this program are awaited with great interest.

While many traditions of medicine are in the process of change the underlying premise remains the same: The primary responsibility of medicine is patient care. If one agrees that the doctor-patient relationship is changing, that the orientation of medical teaching must reflect its new relationship to the community and that medical knowledge must be applied in a team context, then it becomes the responsibility of medicine to develop imaginative new frameworks for patient care.

GEORGE C. ANDERSEN, M.D.

Hermosa Beach

Councilor, Fourth District, California Medical Association

BY DEFINITION, the term *medicine* refers to the healing art (the science and art of preventing, curing, or alleviating disease), and to those substances used to obtain the same.

By association, the term *medicine* means: to the individual, his physician; to society, the organization of physicians; to the planners, health care.

If we are speaking of the physician, he alone can determine the scope of his ability, and with this in mind determine how much responsibility he may safely assume in the care of his patient.

If we are speaking of the organization of physicians, we can only be concerned with (1) maintenance of quality medical care—education; (2) improvement of medical

care—research; and (3) the protection of society from the medically unethical and uninformed, i.e., the charlatans and “quacks,” through exposition.

If we are speaking of total health care, as the planners imply medicine to mean, the physician, individually or as an organization of physicians, enters into a morass of problems which are society-engendered and over which he or his organization has no control and little ability to change.

The physician must be ever alert to the whole patient—biologically, physiologically, and spiritually—to treat him in such a manner as to prevent illness and disability, to restore him to as near a normal state of health as possible, and finally, in the inevitability of impending dissolution, to permit him to leave this life with as much dignity and serenity as possible.

The medical organization must be ever alert to the infringement of third party interference in patient-physician

relationship, medical education, and research. It must be also ready to advise lay organizations and government as to those environmental conditions in society that are inimical to good health, through public information and responsible and adequate representation in those organizations involved.

The health care planners must be aware of the specific needs in society, the lack of which would affect the health of the social milieu, keeping in mind the degree of necessity and the attainability of such programs so developed. Haphazard or incomplete planning leads only to disillusionment and failure.

In the final analysis, however, the primary responsibility rests upon the individual. If he rejects preventive care, does not seek treatment, or will not follow professional advice, all of the resources of the physician, organized medicine, and health plans will be of no avail.

ACTIVE CHRONIC HEPATITIS? — LOOK FOR WILSON'S DISEASE

“You must exclude Wilson's disease [hepatolenticular degeneration] in all patients you think have active chronic hepatitis, because you can do so much good for the patients with Wilson's disease and they can present absolutely identically. So every patient we see under 30 years of age has a slit-lamp for the Kayser-Fleischer ring and a serum copper, urinary copper, and ceruloplasmin, and we look for the changes in the liver biopsy that might suggest Wilson's disease.”

—SHEILA SHERLOCK, M.D., London, England
Audio-Digest Internal Medicine, Vol. 15, No. 17

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EDITORIAL

If One Drug Is Good, Then Two Drugs Are Better?

"If TWO DRUGS, A and B, are administered together, then the net pharmacologic effects may be the same, less than, or more than if A and B had been administered separately." Such a statement accompanied by terms such as antagonism (clear) and potentiation (fuzzy), introduces the subject of drug interaction to students in pharmacology courses. Ordinarily little time is devoted to interactions *per se* and the descriptive pharmacology of single agents occupies the major portion of the instructor's time. However, even superficial perusal of the scientific literature reveals that drug interactions in man are all too common, often with serious consequences. The patient, and especially the in-patient, has become the "laboratory animal" in which most drug interactions have been studied — unfortunately in a retrospective manner. Clearly, this subject must be brought to the attention of all those who have responsibility for drug therapy. Elsewhere in this issue of CALIFORNIA MEDICINE [page 380] Morrelli and Melmon have reviewed much of the literature concerning drug interactions. They stress the importance of knowing the mechanisms of drug action and the variables that influence pharmacologic activity as necessary prerequisites to the understanding of how drugs interact.

The examples of interaction in this review are often those which involve a shift in the dose-response curve of one drug caused by some action of another drug. Since such shifts can and do occur in both directions, it is immediately obvious that in cases where several drugs are administered to one patient the doses of all drugs may have to be adjusted to achieve the maximum therapeutic effect with a minimum of toxicity. Optimal individualization of dosage requires careful observation, calling into question the indiscriminate use of fixed-dose combinations in which two or more drugs are compounded in the same tablet or capsule.

Polypharmacy is a fact. Whether or not patients receiving multiple drug therapy suffer or benefit depends upon the physician's awareness that interactions can occur, his understanding of the pharmacologic properties of the drugs he prescribes, and the availability of up to date information concerning drug interactions in man. Timely review articles such as the one by Morrelli and Melmon in this issue should be of great value to the physician who needs to keep abreast of this rapidly expanding area of drug therapy.

Rising Health Care Costs

HEALTH CARE COSTS are rising. Quite properly this is being viewed with concern, and sometimes alarm, by government, labor and the public who of course must ultimately pay these costs. Physicians, hospital administrators and others in the health care industry are also and properly disturbed. As

might be expected, there is a natural tendency to blame this unpopular state of affairs on someone or something which can be made a scapegoat. There have been allegations and accusations against money-mad physicians, uneconomic hospital practices, inefficient health care delivery systems, unnecessary and excessive union wage increases, and unreasonable demands and expectations on the part of government or the public. A convenient catch-all is inflation, to which almost everyone gives some of the blame. But no one of these scapegoats, nor even all of them together, can account adequately for the rising health care costs. The true cause is far more basic and far less often given its due.

It is suggested that the major rise in health care costs can be traced back to a philosophy engendered by the very expensive but very successful Manhattan Project of World War II. This philosophy states that almost anything can be accomplished if one is willing to spend enough money to get it done. World War II promptly terminated when the atomic bomb became available and was used. The money spent on the Manhattan Project achieved its purpose. A scientific and technologic miracle had been accomplished.

The principle was next applied on a large scale in medical research with the expectation that if enough money were spent, scientific and technologic miracles could also be worked in this field—and this time for the betterment of mankind. Vast sums were contributed from both public and private sources, research thrived, and there were many impressive results. Progress in medical science was dramatic and it was also very well dramatized. The prospect of better health for all was clearly on the horizon for everyone to see and the public responded with rising expectations followed by increasing demands until health and health care are now generally accepted as human rights somehow to be guaranteed by society. But not yet settled is just how this is to be done, what the cost will be, or how it is to be paid for.

As might be expected the principle of the Manhattan Project is once again being applied in the hope that another scientific and technologic miracle can be achieved. Vast sums of money are being pumped into the health care system, again from both public and private sources. The government's focus has been particularly upon the removal of any significant financial barriers to the health care of the aged and the indigent of any age, and to

make sure that this care is rendered to all with equal dignity and within the mainstream of good medical practice. It may be expected that substantial funding will soon become available for manpower procurement and training, for better deployment of knowledge and skills, for equipment and facilities, and for planning regional and community health services. The non-governmental focus has been to develop better programs, quality standards and utilization control within the private sector. The emphasis has been upon accomplishing all this by strengthening the vital pluralistic system which has characterized health care in this nation and encouraging it to plan and experiment to find better and more efficient answers. This is as it should be.

It would seem then that the basic cause of the enormous rise in the amount of money being spent on health care is simply a national decision to spend more money to bring more sophisticated health services to many more people and to do this on a grand scale on the theory that almost anything can be accomplished if one is willing to spend enough money to do it. This does not say that such things as inflation, increases in wages, salaries, fees, cost of living and cost of working, supplies, equipment, facilities and operating overhead do not contribute to these rising costs. But it does suggest that allegations and accusations will do little to help, and that while improvements in economic efficiency and productivity must be sought and put to use, these will by no means be sufficient to control the rising costs of health care. As long as there is a national commitment to make a greater number of more sophisticated and expensive services available to a greater number of better informed and more demanding people, and as long as both the public and the private sector are willing to spend more and more to do this, the amount of money spent on health care will inevitably increase, and thus the costs will continue to rise by any measure and in spite of whatever rhetoric is used. It is time this basic fact is recognized and accepted for what it is by all concerned.

A Recognition Well Earned

THE NORMAN A. WELCH, M.D., Memorial Award was presented to the California Medical Association by the National Association of Blue Shield Plans in recognition of the "scholarly and merito-

rious contribution to the literature of medical economics" made by the CMA's Bureau of Research and Planning.

To this journal the honor that has come to our medical association is the more welcome in that it gives us a chance to add a word or two of our own. Those who guide the workings of the California Medical Association have long recognized that the Bureau is a reliable supplier of the factual information needed for initiating and carrying out the programs and the negotiations of a progressive state medical association. Murray Klutch, director of the Division of Socio-Economics and Research, guides staff efforts in support of the Bureau Activities. The staff is a swift and versatile gatherer of intelligence for the support of either advocacy or defense in contested matters; it is equally able in developing information to permit the association to decide what new directions it ought to be taking. In short, the Bureau frequently makes the difference between wondering and knowing, between fumbling and decisive action, between the wrong course and the right one.

We are pleased that the solid worth we long have recognized almost unconsciously is now deliberately celebrated for what it is.

Carcinoma In Situ of The Uterine Cervix

THIS IS THE 25th anniversary of the publication by Papanicolaou and Traut of the monograph describing the use of vaginal smears for the diagnosis of uterine cancer. The extensive review by Warren Jones [page 353] of the clinical problems which have resulted from this early detection of non-invasive lesions is therefore most timely, and deserves study by all physicians who treat women.

Dr. Jones does not discuss the etiology of cervical cancer, but there are some exciting developments which may prove to be a model for the study of human carcinogenesis. The remote cause is coitus, but the nature of the agent transmitted, whether it be phagocytized DNA fragments of spermatozoa,¹ type 2 herpesvirus hominis² or similar mutogenic material is undecided.

Of more practical immediate concern is the question of how extensively surgical procedures

should be employed for both the diagnosis and the treatment of carcinoma in situ of the cervix. There is little doubt that in our Western states, if not in the United States as a whole, conization has become almost routine in the case of suspicious or positive smears with no visible lesion, yet the detection of invasion is missed in less than 3 percent of cases by the use of multiple "punch" biopsy, an office procedure entailing almost no morbidity. It has also become almost routine to recommend hysterectomy as soon as the diagnosis of in situ carcinoma is made. Dr. Jones points out that at least two-thirds to three-fourths of the patients are cured by ordinary conization. If there are residual lesions they may be readily detected by cytological means during the ensuing six months. Is there ever an indication for immediate hysterectomy?

Unfortunately, so long as total hysterectomy is a "usual and customary" treatment for carcinoma in situ, most surgeons will elect that mode of therapy in preference to a minor procedure followed by a period of prolonged observation. If the latter course results in a cure rate of 94 percent, as Dr. Jones illustrates in Table 2 of his article, then it would appear that hysterectomy actually is required for less than 10 percent of non-invasive lesions. Perhaps it is time for more gynecologists to advocate as well as to practice a more conservative approach to the management of these lesions.

REFERENCES

1. Copleson, M., and Reid, B.: *Obstet. Gynec.*, 32:432, 1968.
2. Josey, W. E., et al.: *Am. J. Obst. & Gynec.*, 101:718, 1968.

Guest Editorial

The Tuberculosis Problem Today

ACCORDING TO POPULAR opinion, tuberculosis is no longer a serious public health problem, yet last year this disease was responsible for more American deaths than the war in Vietnam. Tuberculosis is still a serious problem, but today it is well defined and manageable, in contrast to twenty years ago. Modern medicine provides the scientific knowledge, the medications and the methods adequately to control and ultimately to eradicate the disease in this country. Geographically, tuberculosis in the United States is concentrated in the

older and poorer sections of the urban areas where minority groups and immigrants tend to cluster and live in overcrowded and substandard housing. Approximately 31 percent of the newly reported disease in 1966 was from cities with a population of 500,000 or more, and 45.5 percent of the newly reported patients lived in cities with a population of 100,000 or more.¹

Although morbidity has continued to decline, 47,767 new patients were reported in 1966, with 9,739 or 20.3 percent being less than 25 years of age, and 5,583, or 11.7 percent, less than 15 years. Recent studies indicate that between 20 and 25 percent of the patients with new disease reported annually will be among the recently infected contacts to active communicable tuberculosis, whereas 75 to 80 percent of active cases will develop among the previously infected.² Not all patients under 25 years of age are newly infected, but the proportion of previously infected in this group is so low that the majority in whom clinical disease develops may be presumed to be close contacts to adults with infectious disease. Certainly this is true of the 2,530 tuberculous children under five years of age, and probably also of the 5,583 tuberculous children under 15 years of age.

Tuberculosis was the twentieth leading cause of death in the United States in 1966, with a total of 7,934.¹ Although the age-specific death rate for tuberculosis under 25 years of age has approached zero, 1.5 percent of the children under 15 years of age with newly reported disease died during the year.

It is important to recognize that the majority of new cases and all deaths in children and young adults could have been prevented by currently available chemotherapy and control techniques through a concentrated combined effort by private and public medicine. Thus, 20 percent of the newly reported cases could have been prevented by adequate control measures, including: (1) isolation and treatment of adults with communicable disease; (2) complete chemotherapy regimen for all patients with active or recently inactive disease; and (3) isoniazid chemoprophylaxis of all contacts, converters and reactors in this younger age group. The prevention of infection and disease in children and young adults will also eliminate the reservoir of future adult disease.

Eighty percent of the newly reported disease occurred in adults 25 years of age and older, with 52 percent in the 45 years and older age group.¹

These patients, when their disease is in a communicable stage, are the source of spread and perpetuation of tuberculosis in the community. The majority had been previously infected in their youth, and developed clinical disease by endogenous reinfection when resistance was low and conditions were favorable. Modern drugs can successfully treat 96 percent or more of these patients.

The United States Public Health Service reported that only 47 percent of patients with active disease were in hospital in 1966, and of the patients with active cases at home, only 61 percent had drugs "currently prescribed." Furthermore, 23 percent of those with active cases who remained at home had not been examined for at least one year.³ Thus, decided inadequacies dominate the national picture at a time when scientific knowledge and effective medications are available for successful treatment and control of this disease. The popular misconception that "tuberculosis is licked" is partially responsible, and this must be corrected by an educational program directed toward the medical profession as well as the general public.

Currently 80 percent or more of the medical care for tuberculosis is given outside hospitals. The introduction of isoniazid into the chemotherapeutic regimen was responsible for a pronounced decrease in the length of stay in hospital, due to rapid conversion of the majority of patients to a non-infectious state. It is almost inconceivable that patients with tuberculosis would refuse effective proven chemotherapy. The failure of patients to take medications regularly is not a specific characteristic of any particular group or disease, but is common among patients with chronic illnesses, including diabetes, arthritis and leprosy.⁴ The attitudes which influence the acceptance or rejection of medical care are developed early in life. Although behavioral patterns may be modified, the social and cultural practices of childhood continue to influence the adult. Thus, when patients begin to feel better or become asymptomatic, or when the medicine is disagreeable or the dosage schedule is inconvenient, some will alter the dosage, change the schedule or stop the drugs entirely. Physicians and nurses need look no further than to their own family medicine chests for half-empty bottles and vials of medications which were discontinued by self-evaluation. Education must be pressed continuously to persuade patients of the need for maintaining uninterrupted treatment.

Since 80 percent of the newly reported cases annually develop among the previously infected population, the identification of high risk groups becomes necessary in effective planning for tuberculosis control and prevention. The most effective tool for identifying the previously infected is the tuberculin skin test. Whereas formerly a reaction of 5 mm or more of induration to 5 T.U. of PPD-S, after 48 to 72 hours, was considered positive in survey tuberculin skin testing, this has been recently changed to 10 mm or more of induration for the younger age groups, because of the high prevalence of cross-reactions to infection with atypical mycobacteria among the smaller reactions. Although the majority of 5 to 9 mm reactions are due to infection with atypical mycobacteria, clinical tuberculosis may be present in patients with small reactions or with no reaction at all. Both the small reactors and non-reactors with clinical tuberculosis are usually symptomatic, and they present an entirely different diagnostic problem than survey skin testing. The depression or total absence of a skin reaction in an infected person may be due to certain acute viral infections, such as measles; massive overwhelming tuberculous infection; chronic diseases such as leukemia, Hodgkin's disease and sarcoidosis, and aging. Many elderly persons with small or no reactions to 5 T.U. of PPD-S will frequently have a significant reaction (10 mm or more) if retested two to four weeks

later. It is not known whether the depression or absence of a reaction at the initial testing is due to senile changes in the skin, or the response to the second test is an anamnestic reaction. It does indicate, however, that one must carefully evaluate an apparent skin test conversion in the elderly.

If tuberculosis is to be adequately controlled and ultimately eradicated, all family physicians, pediatricians, and internists should seriously consider the recommendations of Murray in the Medical Staff Conference reported in this issue of CALIFORNIA MEDICINE [see page 390] which clearly defines chemotherapy and chemoprophylaxis from a clinical standpoint. His discussion clearly points out that it is possible to have a generation of tuberculosis-free children and young adults, for the tools are available to prevent infection and disease in the younger population through the proper treatment of patients with clinical disease and the high risk infected groups in the older population.

FRANCIS J. CURRY, M.D.
*Assistant Director of Public Health,
City and County of San Francisco*

REFERENCES

1. Reported Tuberculosis Data — 1966; USPHS, Department of Health, Education and Welfare, Public Health Service Publication No. 638, 1968 Edition.
2. Bulletin of the World Health Organization, Vol. 21, No. 1, 1959, pp. 5-49.
3. Special Tuberculosis Projects, June 1966, Public Health Service, Department of Health, Education and Welfare, Tuberculosis Program, Statistical Services Unit, April 1967.
4. Fox, W.: Self-Administration of Medicaments, Bull. of International Union Against Tuberculosis, Vol. 32, No. 2, p. 307.

California Medical Association



Council Highlights

Highlights of the Actions of the California Medical Association 546th Council Meeting, August 2 to 3, 1968, Los Angeles

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA Headquarters office.

Plans for Health Services Research Center were described by Dr. Lester Breslow of the UCLA School of Public Health. A grant for the center had recently been submitted by UCLA and approved by the U.S. Public Health Service. Dr. Breslow said this center is one of several being developed in the nation, designed to improve the effectiveness and efficiency of personal health services through research and demonstration. The focus of the project is on development of criteria for evaluating the center's work which will also include observation (application of the criteria in measurement of outcomes of current systems and practices of health care); experimentation and innovation (deliberate modification of elements in the practices and systems of health care with a view toward improvement of effectiveness and efficiency); and studies of implementation (investigation of institutional, legal and other social problems inherent in moving from single demonstrations of new practices or system modification to widespread adoption in the general community).

Council voted to request CMA representation on the policy-making committee of the California Health Services Research Center.

Consultants to Extended Care Facilities were requested from CMA to serve as committee members or resource persons to the Project for Consultants to Extended Care Facilities. This Project's purpose was set forth as being to develop a guide and workbook for professional health con-

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3345 Wilshire Blvd., Suite 500, Los Angeles 90005 • 213 380-8272
RICHARD W. LEMOS Sacramento Office
1127 11th St., Sacramento 95814 • 916 444-7496

sultants who give consultation to patient care policies to extended care facilities, funded through the U.S. Public Health Service, with the California Nurses' Association as contractor.

Council voted to appoint Drs. Pierre Salmon, Thomas N. Elmendorf, William F. Kaiser, Joseph P. O'Connor and Charles E. Schoff, Jr., to serve as committee members or resource persons on this project.

Formal and Continuing Liaison by the CMA Commission on Public Agencies to the Department of Professional and Vocational Standards was requested by action of the Council.

On another subject, Council also voted to request the CMA Scientific Board to study the problem of quackery in obesity treatment programs and to report back to the Council with its recommendations.

Health Forum Series of one-page health information articles published for 20 weeks in the *San Francisco Examiner* was commended by resolution of the Council, which expressed its appreciation to the 25 physicians contributing to the preparation of these articles, and requested that these physicians be sent this resolution of commendation for their service in the public interest.

Professional Liability Problems were discussed pertinent to the CMA study, "Should CMA Form a Physician-Owned or Controlled Malpractice Carrier?" The Medical Review and Advisory Committee recommended that the study be approved and given immediate and wide dissemination.

Council voted to approve the study and request wide and immediate dissemination.

Pilot Project on Patient Arbitration was presented on recommendation of the Medical Review and Advisory Committee. Under a proposed California Hospital Association program, a new paragraph would be added to the regular hospital admission form stating that the patient agrees to subject any dispute with the hospital to arbitration under the rules of the American Arbitration Association and the special rules of the California Hospital Association. The committee's specific recommendations, as approved by Council, were:

(1) The proposed two-year project be instituted in a few selected Los Angeles hospitals which are prepared to undertake this type of experiment; (2) The program involve the hospital medical staffs who would be given an advance opportunity to join in the arbitration agreement; and (3) CMA appoint an advisory committee to work with a similar committee of CHA in overseeing the arbitration project.

Council then voted to appoint Doctors Lewis T. Bullock (chairman), Joseph F. Boyle and John B. Dillon to the CMA advisory committee on this project.

A Report on Dangerous Drugs was presented by CMA Speaker of the House of Delegates, Dr. William F. Quinn, who told Council that an excellent motion picture on dangerous drugs was showing at the Museum of Health in Los Angeles. Council voted to send a letter of commendation for this activity to the Los Angeles County Medical Association and Dr. Norman Sprague for this excellent effort.

The Insurance and Prepayment Committee of CMA presented a progress report on the development of a statement on "Guidelines to Component of an Adequate Program of Health Care Coverage." Committee Chairman Ralph W. Burnett, M.D. also stated that his committee felt that although CMA will be represented on the technical advisory committee of the California Council for Health Plan Alternatives, and will be engaged in continuing discussions with the organization, it felt that it should go further by taking the initiative in inviting CCHPA representatives to meet with the committee.

Council voted to authorize the Committee on Insurance and Prepayment to extend an invitation to representatives of the CCHPA to meet with it in the near future.

CMA Community Health Services Commission requested Council endorsement of the National Safety Council's design for a symbol for slow-moving vehicles, and CMA support of legislation which would make mandatory the use of the symbol on vehicles traveling 25 miles an hour or less. Council approved these two recommendations.

Community Health Services Commission Chairman Dr. Marvin Shapiro also asked that an intensive statewide study of the incidence of hepatitis be conducted by the Bureau of Research and Planning.

Council voted to request the Bureau of Research and Planning to conduct the study on the incidence of hepatitis in California, and the development of this study to be coordinated with the CMA Committee on Blood Banks.

The CMA Scientific Board report presented by Chairman Charles J. Tupper, M.D. was followed by action on four recommendations to Council. The Council voted: (1) to approve the appropriateness of seeking funding for the publication "What Goes On" which lists postgraduate education meetings through the California Committee on Regional Medical Programs; (2) to approve training guides for personnel in coronary care units (copies of these guides may be obtained by writing CMA); (3) to approve the Third National Cancer Survey to be conducted by the Public Health Service's National Cancer Institute, National Institutes of Health; and (4) to approve special educational programs in two areas.

CMA Finance Committee recommendations presented by Committee Chairman Dr. Harold Kay

were approved by Council. The Council voted: (1) to request the Executive Committee to evaluate the structural and financial aspects of CMA government relations activities and report back to Council with its recommendations; (2) to request the Executive Committee to study the recommendation that a policy be established that no Commission or Committee may have or maintain a separate checking account and report back with recommended action; (3) to establish policy that the chairman of any Committee or Commission designated by Council to report and be in attendance at Annual Session shall be reimbursed for travel and \$35.00 per diem (so long as this is the sole reason for attendance); (4) to increase the portion of the dues income allotted to *California Medicine* from \$3.00 to \$4.00 per member for the 1969-70 budget; (5) to increase subscription prices for *California Medicine* from \$6.00 to \$8.00 per year for non-members; and (6) to approve an allocation against surplus funds for the fiscal year ending 1968-69 to be made in the amount of \$1,085 to cover the budget for the Committee on Alcoholism.

Intracaths and the Role Of the Registered Nurse

A Joint Statement by the California Medical Association, the California Nurses' Association and the California Hospital Association

SINCE THE USE OF intracaths in starting intravenous infusion has arisen since the issuance of the Joint Statement on the Role of the Registered Nurse in Starting the Administration of Intravenous Fluids, this Joint Statement is presented by the California Medical Association, the California Nurses' Association, and the California Hospital Association.

1. The registered nurse may use intracaths in starting the intravenous administration of fluids only if the registered nurse has had special competent instruction in the use of intracaths.

2. The registered nurse uses intracaths upon the order of a licensed doctor of medicine.

3. The order relates to a specific patient.

4. In an institution or agency where a registered nurse is to use intracaths to start the administration of fluids, there shall be a committee, composed of representatives from the Medical Staff, the Department of Nursing, and Administration, to determine:

- a) what preparation is required of a registered nurse to use intracaths.
- b) what inservice teaching or preparation is required.
- c) which registered nurses in the facility are so prepared.
- d) what types of intracaths may be used.

5. The framework of the committee, the framework of the preparation of the registered nurse, and all the pertinent criteria shall be reproduced in writing and made available to and invited to the attention of the total medical and nursing staff.

June 15, 1968

Proposed CMA Constitutional Amendment

FOR ACTION IN 1969

One Constitutional amendment was introduced in the 1968 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. The language in parenthesis is to be deleted. In addition, the proposed Constitutional amendment is required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

1 1 1

CHARTERS, ARTICLE I, SECTION 5

Constitutional Amendment 1-68

Committee 4

Introduced by: The Council

Resolved: That Article I, Section 5 of the Constitution of this Association be amended by deleting the language in parentheses, so that the section will now read:

Section 5.—Component Society Charters

Charters to component societies may be granted and revoked as hereinafter prescribed. (, subject to the limitation that only one charter may be outstanding at any one time in any county.)

(Notwithstanding the foregoing,) One charter may be issued to a component society that is not limited as to geographical area or which overlaps the area covered by one or more existing component societies.

In Memoriam

BARNETT, ANNA FRANKLIN, Palo Alto. Died 12 September 1968, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Doctor Barnett was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



BUCKLEY, PHYLLIS ELAINE, Fremont. Died 16 September 1968 in Fremont of metastatic carcinoma of the breast, aged 43. Graduate of University of Colorado School of Medicine, Denver, 1955. Licensed in California in 1957. Doctor Buckley was a member of the Alameda-Contra Costa Medical Association.



CRANE, W. WHITFIELD, Oakland. Died 15 September 1968 in Oakland of coronary artery thrombosis, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Doctor Crane was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



FLESHER, ROY EMMETT, Redlands. Died 4 September 1968 in Redlands, aged 77. Graduate of Chicago College of Medicine and Surgery, 1917. Licensed in California in 1923. Doctor Flesher was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



FRASER, LEOPOLD H., Richmond. Died 30 September 1968 in San Pablo of cerebrovascular accident, aged 70. Graduate of Boston University School of Medicine, 1923. Licensed in California in 1925. Doctor Fraser was a member of the Alameda-Contra Costa Medical Association.



FREEMAN, MURRAY TAYLOR, San Bernardino. Died 31 August 1968 in San Bernardino, aged 47. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1945. Licensed in California in 1949. Doctor Freeman was a member of the San Bernardino County Medical Association.



GRAY, ROSCOE NELSON, Oakland. Died 7 September 1968 in Oakland, aged 75. Graduate of Oakland College of Medicine and Surgery, Oakland, 1918. Licensed in California in 1918. Doctor Gray was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

HENDERSON, ROBERT G., Long Beach. Died 28 August 1968, aged 79. Graduate of University of Michigan Medical School, Ann Arbor, 1911. Licensed in California in 1914. Doctor Henderson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



HUMBERT, JAMES, Westminster. Died 8 September 1968 in Los Angeles, aged 76. Graduate of University of Louisville School of Medicine, Kentucky, 1917. Licensed in California in 1946. Doctor Humbert was a member of the Orange County Medical Association.



KORNGOLD, HERBERT W., Sacramento. Died 21 September 1968, aged 51. Graduate of University of Illinois College of Medicine, Chicago, 1941. Licensed in California in 1947. Doctor Korngold was a member of the Sacramento County Medical Society.



LINDEMULDER, FRANKLIN GERRITT, San Diego. Died 8 September 1968, aged 66. Graduate of University of Louisville Medical School, Ann Arbor, 1928. Licensed in California in 1933. Doctor Lindemulder was a member of the San Diego County Medical Society.



LYONS, JOHN BARKS, Los Angeles. Died 12 September 1968 in Los Angeles, aged 48. Graduate of Howard University College of Medicine, Washington, D.C., in 1944. Licensed in California in 1952. Doctor Lyons was a member of the Los Angeles County Medical Association.



MONSON, LAFAYETTE PARKINSON, San Francisco. Died 5 October 1968, aged 66. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1925. Licensed in California in 1930. Doctor Monson was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



OKAMI, SHIGEICHI, Long Beach. Died 16 September 1968 in Long Beach of heart disease, aged 72. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1925. Licensed in California in 1925. Doctor Okami was a member of the Los Angeles County Medical Association.



SMOOT, JR., JOSEPH M., San Pedro. Died 25 August 1968, aged 57. Graduate of New York University College of Medicine, New York City, 1947. Licensed in California in 1948. Doctor Smoot was a member of the Los Angeles County Medical Association.

1969 ANNUAL SCIENTIFIC ASSEMBLY

OF THE CALIFORNIA MEDICAL ASSOCIATION

Ambassador Hotel
Los Angeles, March 15-19

Three general meetings focus on:

RECOGNITION AND TREATMENT

- **STROKE**
- **NEONATAL AND CONGENITAL DISEASES**
- **METABOLIC DISEASES**

RENOWNED SPEAKERS ARE:

ROBERT A. ALDRICH, M.D.

Professor and Head
Division of Human Ecology
Department of Pediatrics
School of Medicine
Director, Health Resources Study Center
University of Washington

ROBERT D. BLOODWELL, M.D.

Chief of Pediatric Surgery Section
Department of Surgery
Assistant Professor of Surgery
Baylor University College of Medicine

BARTON CHILDS, M.D.

Professor of Pediatrics
Johns Hopkins University
School of Medicine

CLARK H. MILLIKAN, M.D.

Senior Consultant
Department of Neurology
Mayo Clinic
Professor of Neurology
Mayo Graduate School of Medicine
(University of Minnesota)

JOSEPH E. RALL, M.D., Ph.D.

Director of Intramural Research
National Institute of Arthritis & Metabolic Diseases
National Institutes of Health

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS

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Health and Family Life Education
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↑
TO HARBOR FWY. 11



SEVENTH

Catalina

Kenmore

CLAYLORD

Alexandria

WILSHIRE BLVD.

CMA 98th annual session



The Ambassador

EIGHTH

↑
TO VERMONT ST.
AND SANTA MONICA FWY. 10

Mariposa Ave.

SEVENTH



NORMANDIE



Sheraton-Wilshire

Ardmore

Irolo St.

CMA

98th annual session • march 15-19

application for **HOTEL ACCOMMODATIONS**

NINETY-EIGHTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 15-19, 1969

AMBASSADOR HOTEL, LOS ANGELES

**House of Delegates Opening Session, Ambassador Hotel, Saturday evening, March 15;
Scientific Sessions, Ambassador Hotel, begin Sunday morning, March 16.**

1. Fill in the form below *completely* for room accommodations at the CMA's 1969 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, Ambassador Hotel, 3400 Wilshire Boulevard, Los Angeles 90005 by *February 17, 1969*.

	Single	Double and Twin	Suites
AMBASSADOR HOTEL 3400 Wilshire Boulevard	\$14-16	\$18-22	\$45-70
SHERATON-WILSHIRE HOTEL 3515 Wilshire Boulevard	\$14-16	\$18-22	\$45-70
CHANCELLOR HOTEL 3191 West Seventh Street	\$14-16	\$18-22	\$45-70
GAYLORD HOTEL 3355 Wilshire Boulevard	\$14-16	\$18-22	\$45-70

SEND TO: California Medical Association Housing Bureau
Ambassador Hotel, 3400 Wilshire Boulevard, Los Angeles 90005

Please reserve the following accommodations for the CMA's 1969 Annual Session in Los Angeles, March 15-19.

Single Bedroom \$..... Twin-Bedded \$..... Double Bed \$..... Suite \$.....

First Choice Hotel..... Second Third.....

Arrival (date)..... Hour.....^{a.m.}_{p.m.} Departure (date)..... Hour.....^{a.m.}_{p.m.}

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: Officer?..... Delegate?..... Alternate?..... Speaker?.....

Address: County

City and State..... Zip Code.....

GUESTS' NAMES AND ADDRESSES:

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.

Director, State Department of Public Health

A Clinical Laboratory Improvement Program for California Laboratories

IN RECENT YEARS, professional, technical and popular publications have vigorously criticized the performance of the nation's clinical laboratories, making charges ranging from unreliability of laboratory tests to outright fraud. Concern over these criticisms is reflected in the passage of recent Congressional legislation regulating laboratories in interstate commerce and in the Medicare program.

Demands for improvement of clinical laboratory performance can be met. We now have well-developed techniques for measuring and evaluating the quality of laboratory performance by means of intralaboratory quality control and proficiency testing.

Intralaboratory quality control consists of continuous surveillance by the laboratory director and his staff of all factors which may influence the reliability of test results. Basic features include the use of standards of known content in calibrating equipment, and monitoring the daily testing activities. Properly performed, quality control provides daily information concerning the reliability of the results and performance of laboratory instruments.

Proficiency testing involves the examination by the laboratory of "unknown" specimens prepared and submitted by an outside organization. The results are then submitted to the outside organization, which compares them with results achieved on the same specimens by reference or other participating laboratories. Proficiency testing shows how performance in a laboratory compares with that of reference or peer laboratories. For the state agency, it can also indicate what laboratories may

be in most need of improvement, where training is needed and what subject areas require better methods.

Medicare regulations require that all independent laboratories (about 600 in California) maintain an intralaboratory quality control program acceptable to the state agency which administers state and federal laws applying to clinical laboratories — the State Health Department in California. And approximately 300 of these independent laboratories whose directors cannot meet certain requirements must participate in a state-operated or state-approved proficiency testing program. To implement these requirements, the department approved testing services developed by such professional organizations as the American Association of Bioanalysts and the College of American Pathologists.

Recently, laboratories and professional associations in this state have exerted pressures to establish uniform state laboratory laws by applying quality control and proficiency testing procedures to all laboratories as a condition of licensure. At present, however, application of quality control and proficiency testing techniques is largely voluntary.

California's physicians have fostered high standards of clinical laboratory performance for many decades. Physicians, laboratory directors and technologists began to participate in voluntary systems of laboratory certification in 1923. Long before the enactment of federal laws, they inspired and supported California's Clinical Laboratory Act of 1938, which made this state one of the few having comprehensive laws regulating clinical laboratories and setting standards. Laws and standards are still in effect, although they have been revised since that time.

State law requires that all clinical laboratories except those operated by the federal and state governments or by an individual physician for his own patients, must be licensed by the State Health Department. Currently there are 1,480 licensed laboratories in the state, of which approximately 500 are in hospitals.

The department annually conducts two rigorous examinations for laboratory personnel licenses, and has held as many as 30 workshops a year in specific areas of laboratory work. In September of this year, over 600 persons attended seminars in laboratory performance evaluation on two successive days in eight different locations in the state, under the sponsorship of the California Committee on Training in Medical Laboratory Sciences and in cooperation with professional societies and the State Health Department.

Three advisory committees assist the department's Division of Laboratories: an Advisory Committee on Clinical Laboratory Technology, concerned with education and experience standards of laboratory personnel and the legal aspects of the clinical laboratory law; an Advisory Committee on Clinical Laboratory Performance Evaluation, which assists in establishing standards for quality control and proficiency testing; and a committee to coordinate all state-wide training of laboratory personnel.

In the near future adequate controls must be established with respect to the use of automated

laboratory equipment which will require more skill and education on the part of laboratory personnel. Automation will coincide with increased numbers of determinations which laboratories will be asked to run for multiphasic and single-category screening programs, especially in conjunction with increased emphasis on preventive medicine.

In the knowledge that well-tested techniques for assessing quality and maintaining high standards of laboratory services are available, the practicing physician should insist upon technical excellence in his clinical laboratory. He should also be aware of testing programs which can improve performance and control the quality of laboratory work in his office laboratory and should apply the same standards as are applied in other clinical laboratories, hospital and independent, in the state.

Physicians can in this way continue to contribute to improvement of clinical laboratory standards and performance which have made laboratory results in this state among the most consistently reliable anywhere in the nation, offering protection to physicians and patients alike.

CARDIAC ARREST AND DEPRESSED pH

"I have a strong hypothesis which is purely a theory, but I've not yet had it disproved: cardiac arrest cannot be induced with a normal pH in the absence of a gross overdose of something like fluothane. . . . Virtually all of the acute origin of cardiac arrest is superimposed upon a circulatory status in which pH is already depressed. . . . We have not yet found an individual with a normal pH in whom the heart could be arrested.

"The values for central venous blood pH are very predictable. In an operating room or in an awake patient, they are virtually never under 7.3, and a useful figure for your memory is that anything under 7.3 is abnormal. It's not very abnormal, but it's not normal, and it indicates that something is awry. . . . We use pH values as a screening mechanism: as long as the numbers are above 7.3, the situation is usually satisfactory; when they drop below this point, we start looking for a reason."

FRANK C. SPENCER, M.D., New York City
Audio-Digest Surgery, Vol. 15, No. 19



WOMAN'S AUXILIARY

to the California Medical Association

The Courier

THIS HAS BEEN another successful year for the *Courier*, published quarterly for all members of the Woman's Auxiliary to the California Medical Association.

Emphasis has been on news of the county auxiliaries, especially those programs entirely new in concept, new in that community or, more frequently, a new slant on an old and tried idea. Thus, our readers read this past year of Contra Costa county adopting the Meals-On-Wheel program so successful in San Francisco for many years; the "Pixie Postcard Sale" held in Shasta-Trinity, a trademark printed on packages of postcards; the workshops held at the Monterey-San Benito Health Careers Day to acquaint high school counselors with the concept of the whole Health Team, not only of those students with R.N. and M.D. potential; the one-day GEMS babysitting course given in San Mateo; the Health Careers Assembly held by San Diego on the carrier *Ticonderoga*; and numerous other ideas from throughout California.

Physician's wives and children with a variety of interests have been the subjects of profile sketches over the past three years under the present *Courier* editors. Some of these, as well as some of the county news, have been picked up by the national publication for auxiliary members, *M.D.'s Wife*.

This past year these included, "Operation Big Top," the story of efforts by Mrs. Leo Snyder of Fresno to have underprivileged children attend the circus; and a story about Karin Hutchinson, talented young pianist from San Mateo county now studying in Paris under the sponsorship of Philippe Entremont.

About the time that this article appears in the journal of the California Medical Association, your wives will be reading of the wife of a past CMA president, a nationally known lecturer and photographer of conservation and wildlife movies; and of the harrowing escape from Czechoslovakia in 1938 of a current county auxiliary president — timely in view of the current crisis in that country.

If any of the physicians who read this page know of medical families in California who would make interesting subjects for future articles in *Courier*, they may help indeed by contacting any of the undersigned editors. There must be a wealth of untapped stories concerning M.D.'s, their wives and children. We rely on you.

Mrs. Harry Alton, Editor, *Courier*
333 Bridge Road
Hillsborough, Ca. 94010

Mrs. Harry Dvorsky, Co-Editor
2657 Vista Grand Court
San Leandro, Ca. 94577

Mrs. P. Wilson Matlock, Contributing Editor
4076 North Van Ness Boulevard
Fresno, Ca. 93704

Mrs. Albert Warrens, Contributing Editor
2190 North Avenue
Chico, Ca. 95926

NEWS & NOTES

STATE • COUNTY

LOS ANGELES

Two-year research fellowships in oncology and cancer chemotherapy and one-month fellowships in various aspects of cancer for practicing physicians are available at the University of Southern California School of Medicine. The long-term and the short-term fellowships are under different departments but both are sponsored by the National Cancer Institute.

The one-month postgraduate fellowships in cancer for practicing physicians are available immediately. They carry a stipend of \$1,500. Separate programs are available in tumor surgery, tumor pathology, radiation therapy, and medical oncology. Applicants should be board eligible or board certified and should submit a brief résumé of their professional background to Arthur J. Donovan, M.D., Program Director, Cancer Teaching, School of Medicine, University of Southern California, 2011 Zonal Avenue, Los Angeles, California 90033.

The two-year clinical research fellowships in oncology and cancer chemotherapy will begin 1 July 1969. Fellows will have broad patient responsibility and will supervise three residents and two interns. The Oncology Service comprises 30 beds plus an active outpatient clinic. Both standard and investigational chemotherapy is carried out under supervision of the Western Cooperative Cancer Chemotherapy Group. If desired, the fellowships can include a three-month rotation on the Hematology Service of Los Angeles County—USC Medical Center. A year of fellowship can substitute for a year of residency for board eligibility. The stipend for the first year is \$6,000, of which \$3,600 is tax-free, and additional allowance is made for dependents and advanced status. Applicants should have completed at least one year of approved medical residency and be eligible for a California license. They should send a brief résumé to David C. Stolinsky, M.D., USC School of Medicine, (Oncology Service) 2825 South Hope Street, Los Angeles, California 90007.

Dr. Neal C. Hamel, Encino, was elected to a one-year term as president of the Flying Physicians' Association during the organization's 14th annual meeting.

* * *

Three Los Angeles laryngologists on the faculty of the University of Southern California have been honored by the award of the Manuel Garcia prize. Drs. Hans von Leden, Naoaki Yanagihara and Yasuo Koike were selected by an international panel of specialists for their scientific contributions at the Institute of Laryngology and Voice Disorders in West Los Angeles. This prize was established several years ago by the Sandoz Foundation in Switzerland in memory of Manuel Garcia, the Spanish discoverer of the laryngeal mirror. The Los Angeles scientists were selected for their development of new and more accurate diagnostic techniques in the field of laryngology.

ORANGE

The appointment of two heads of departments of University of California, Irvine, College of Medicine, has been announced by Dean Warren L. Bostick. Henry Wood Elliott, M.D., Ph.D., was named professor and chairman of Medical Pharmacology and Therapeutics, and Edward R. Arquilla, M.D., Ph.D., professor and chairman of Pathology.

Dr. Elliott, formerly professor of pharmacology at University of California San Francisco Medical Center, succeeds Robert W. Earle, Ph.D., who will return to full-time teaching and research.

Dr. Arquilla came to Irvine from UCLA School of Medicine, where he was professor of pathology.

SAN FRANCISCO

The annual Dr. J. Elliot Royer Award was given this year to Dr. Alexander Simon, director of the Langley Porter Neuropsychiatric Institute. Presentation of the certificate of award and a \$10,000 check was made on behalf of the Regents of the University of California by Dr. Henry Gibbons, III, president of the San Francisco Medical Society.

The Royer award was established under the terms of the will of the late Dr. J. Elliot Royer. It was his wish that each year a medical person in the San Francisco Bay Area be recognized for the most significant contribution to the advancement of psychiatry and neurology.

A grant of \$335,000 for development of an Anesthesia Program Project was made to the University of California San Francisco Medical Center by the National Institute of General Medical Sciences, Department of Health, Education, and Welfare.

Under the direction of Dr. William K. Hamilton, professor and chairman of the Department of Anesthesia, the new project is part of a national program to expand research and training in all aspects of modern anesthesiology. A major aim is to increase the number of anesthesiologists needed to meet the demands of both clinical and academic medicine.

* * *

Dr. William J. Rutter, currently professor of biochemistry and genetics at the University of Washington, has been named chairman of the Department of Biochemistry at the University of California San Francisco Medical Center.

Dr. Rutter was the recipient of the 1968 American Chemical Society Award in Enzyme Chemistry. The award is given in competition to the biochemist under 40 years of age who is judged to have made the most outstanding contribution to enzymology.

SANTA CLARA

Dr. Jordan R. Wilbur, formerly an assistant professor of pediatrics at Stanford School of Medicine, has been appointed head of the Department of Pediatrics at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston.

VOLUNTEER PHYSICIANS FOR VIETNAM

The following is a statement by the President of the United States on the arrival of the 500th physician volunteer in South Vietnam, 12 August 1968. Names of the 68 California physicians who have served in that three-year period are listed at the end of the statement.

Three years ago South Vietnam welcomed the first American physician to volunteer for service in a Vietnamese civilian hospital. He was Dr. Richard E. Perry of St. Petersburg, Fla. This program was designed to relieve the suffering of civilians in a country suffering from a severe shortage of medical manpower.

Today, the 500th physician volunteer arrives in South Vietnam as a member of the American

Medical Association's Volunteer Physicians for Vietnam program. Dr. Philip A. Pritel of Vancouver, Wash., is one of seven American doctors arriving today [August 12] at Saigon's Tan Son Nhut Airport almost on the third anniversary of Dr. Perry's arrival in 1965.

Volunteer Physicians for Vietnam is a response to a plea from the South Vietnamese Government and people for medical aid. Supported by funds from the U.S. Agency for International Development, it is administered by the American Medical Association.

Physician volunteers serve two months without pay in Vietnamese civilian hospitals. This is an example of true American ideals.

Physician volunteers have come from 49 States, the District of Columbia, the Canal Zone, and seven overseas posts. Fourteen women have served. Twenty-five doctors have served two tours, and five have served three times in this program. Twelve volunteers have returned to Vietnam as long-term employees to support the U.S. Medical Mission. Two former volunteers are preparing to return to Vietnam as medical missionaries.

Recruitment continues as the need in Vietnam continues; 32 physicians are needed every 60 days to maintain the program at its current strength.

The unselfish example demonstrated by these doctors makes us all proud of our American heritage of aiding the oppressed.

Robert E. Adler, Fremont
Sergio E. Betancourt, San Francisco
James V. Bradley, Pinedale
Merritt C. Canfield, San Diego
Paul L. Carlson, Modesto
Lawrence O. Carpenter, Point Arena
Bernard W. Casselman, Los Angeles
James G. Cavanaugh, Sacramento
William B. Chastain, Empire
Philip H. Clinkston, Vallejo
Grange S. Coffin, Eldridge
Lloyd H. Cotter, Santa Ana
Howard Detwiler, Van Nuys
Wade R. Eckert, Mammoth Lakes
Lloyd W. Espen, Redwood City
Neal R. Fisher, Covina
George W. Flynn, Petaluma
Stanley M. Garstka, Bakersfield
Ralph G. Gayton, El Monte
Vernon R. Gee, Redding
John W. Godsey, San Francisco
Jack D. Halpin, Los Angeles
Oril S. Harbaugh, San Diego
William A. Harris, Los Angeles
Allen Hassan, Talmage
William M. Helvey, Sunnyvale
Wayne A. Hemphill, Victorville
Thomas Humphrey, Los Angeles
Roland K. Iverson, Marysville
James Jones, San Jose
Charles Keagy, Delano
Richard F. Keiger, Vacaville
Robert M. Kradjian, San Francisco
Gilbert Lee, Los Angeles

William P. Levonian, Santa Cruz
Marvin Lottman, Anaheim
Russell H. Lowell, San Diego
David L. McAninch, Glendale
William H. Marshall, Jr., Stanford
William J. Martin, Ventura
Arthur Miller, Hollywood
William B. Neal, Jr., Los Angeles
Charles A. Owen, San Francisco
James H. Phelps, Upland
Jesse C. Ralph, Sacramento
Richard C. Reznicek, Torrance
Henry N. Ricci, Martinez
Thomas V. Rielly, San Diego
Robert B. Rowe, Madera
Karl D. Ruppert, Sacramento
Joost Sluis, San Francisco
Gabriel Smilkstein, Claremont
Lawrence A. Smookler, San Francisco
Roger A. Thill, Harbor City
Lloyd C. M. Thom, San Leandro (Washington)
Harry E. Tucker, Chino
Edward S. Vanderhoof, San Rafael (USAID)
Donald S. Weaver, Sacramento
E. Robert Wells, Glendale (U.S. Army)
Leo L. Wenke, Healdsburg
Robert L. Wick, Jr., Los Angeles (Ohio)
Hal T. Wilson, San Bernardino (Vietnam)
William E. Woodruff, Vallejo
Ralf Young, Long Beach

The Physician's BOOKSHELF



CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried on page 58 of the Advertising Section.

PLANT TOXICITY AND DERMATITIS—A Manual for Physicians—Kenneth F. Lampe, Ph.D., Professor of Pharmacology, School of Medicine, University of Miami, and Rune Fagerstrom, Pharm. Dr., Director, Central Hospital Pharmacy, Uddevalla, Sweden. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, Md. (21202), 1968. 231 pages, \$9.25.

The first section of this manual is devoted to a discussion of Emergency and Supportive care in patients who have ingested plant material. Treatment is prescribed primarily on the basis of symptoms as is necessary when the identity of the plant is not known.

Indications for and means of emptying the stomach are reviewed.

One may sometimes identify the toxic material by the symptoms it causes. A table listing 21 symptoms and indicating which ones are to be expected in poisoning by the commoner offending plants is shown inside the front and back covers.

In the main body of the manual, toxic plants are classified as follows: 1. Gastroenteric irritants; 2. Those producing cardiovascular disturbances; 3. Plants having nicotine-like action; 4. Atropine-containing plants; 5. Those acting primarily on the central nervous system; 6. Cyanogenetic plants (those releasing hydrocyanic acid); 7. Liver-damaging plants; 8. Poisoning by mushrooms; 9. Miscellaneous poisonous plants.

These major classes are further divided into groups which have the same or related toxic agents and effects. These groups and, in most instances, individual plants are then discussed according to toxicology and chemistry, symptoms, prognosis and treatment. Both botanical and common names are given and each plant is described. In addition to a written description, 78 of the plants are represented by full page black and white drawings.

Numerous case histories are presented in the text.

The final section of the manual deals with the more important aspects of dermatitis and keratoconjunctivitis due to plants.

Some may cause mechanical injury as from spines or serrate edges. Others contain substances which are directly irritating to the skin. Exposure to many may result in allergic reactions. Some may cause combinations of mechanical, direct chemical and allergic dermatitis. These categories are listed and discussed.

Major attention is given to the background and differential diagnosis of allergic contact dermatitis. The use and limitations of patch-testing and treatment are dealt with briefly. Pollen dermatitis and photodermatitis are given special consideration and plants causing these reactions are listed. At the end of this section, there is a long list of dermatitis-producing plants indexed to an extensive list of references on the subject.

The bibliography at the end of each of the chapters is an important part of the manual.

Asthmatic effects are not covered.

Careful selection and organization of material and brevity are noteworthy.

There are 231 pages of about 7" x 10". Cover, paper, type and readability are excellent.

The manual is well indexed and the illustrated drawings are noted in the index in bold numbers.

I believe this work deserves wide distribution in medical libraries and among individual physicians. Those in general practice, pediatrics, internal medicine, dermatology, and, in fact, most of the medical specialties will find it interesting and useful.

H. V. ARLINGTON, M.D.

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RADIOACTIVE NUCLIDES IN MEDICINE AND BIOLOGY: MEDICINE—Third Edition—Solomon Silver, M.D., Consulting Physician; Chief (Emeritus), Thyroid Clinic, The Mount Sinai Hospital; Clinical Professor of Medicine (Physics) and Acting Director, Andre Meyer Department of Physics, The Mount Sinai School of Medicine of the City University of New York. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1968. 539 pages with 82 illustrations, \$12.50.

As in the previous two editions of this book, the presentation of the material is lucid and concise. The basic physics as related to the clinical use of radioactive isotopes is not included, but the companion volume of the previous edition by Quimby and Feitelberg will also serve as a source of reference for this third edition. An updated third edition on the basic physics, and especially instrumentation, will be welcomed.

There is uniformity in the presentation of the various topics which are now referred to as nuclear medicine. As in the previous edition, the clear and informative figures remain with few changes. On the other hand, being a single-authored book in what is today a very big field, the book lacks the originality of presentation of topics which one finds in a multi-authored book written by researchers and specialists. The major part of the book, which deals with the thyroid gland and its related functions, is exhaustive and the authorship by one with special interests in the subject is recognized.

The number of pages has increased from 347 in the second edition to 539 in this third edition. No chapter has been eliminated and every chapter has been increased in length by between one and 43 pages. The first five chapters relate to thyroid function and constitute about 45 percent of the book. It may be that this is an overemphasis of this area of nuclear medicine as it is applied today, but this is not a serious criticism. Less than 8 percent

of another recent book on nuclear medicine is devoted to thyroid and its related function. Unfortunately the sections on the thyroid have not been completely rewritten in the present volume, but instead paragraphs have been added here and there to bring them up to date.

Two new chapters have been added. One of these is in the important area of studies of the central nervous system and the other relates to the lung function. Both of these chapters are useful additions of subjects which were only mentioned in the chapter on "tumor localization" of the second edition. No scintillation camera pictures are shown; this is an unfortunate omission in the coverage of a new method of instrumentation which is becoming so widely used today.

Another useful addition is "Appendix B: Diagnostic and Therapeutic Uses of Radioisotopes in Medicine." This is a useful table arranged according to organ or function of interest. It will serve as a reference for the selection of procedure to consider in the study of a disease state.

Every physician will find some sections of this book of interest. It should be available in every hospital medical library and physicians who have the services of a laboratory of nuclear medicine will find a copy useful on their bookshelf.

LARRY W. McDONALD, M.D.

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NOYES' MODERN CLINICAL PSYCHIATRY—Seventh Edition—Lawrence C. Kolb, M.D., Professor and Chairman, Department of Psychiatry, College of Physicians and Surgeons, Columbia University; Director, New York State Psychiatric Institute and Psychiatric Service, Presbyterian Hospital of New York. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 638 pages, \$9.00.

This book for a long time has been one of the widely used better textbooks of psychiatry. This Seventh Edition (revised by Dr. Lawrence C. Kolb) has attempted, as have previous editions, to keep current with the advances and changes in psychiatry. A new chapter has been added on the neurophysiology of behavior. It includes some of the recent studies of sleep. A new section has been added on the behavior disturbances caused by hallucinogenic drugs and the chapter on psychiatric reactions due to cerebral arteriosclerosis and senility has been updated. Behavior therapy and family therapy are included in the discussion of psychotherapy and minor changes have been made in many other areas to bring all chapters up to date.

The style is clear and easily readable. The book is recommended to all physicians as an excellent standard textbook of psychiatry for reference purposes and to students for basic orientation to the subject.

NORMAN Q. BRILL, M.D.

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CARDIAC RADIOLOGY—Edward F. Dunne, M.B., B.Ch., Department of Radiology, St. Vincent's Hospital, Los Angeles, Calif. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1967. 256 pages, \$12.50.

This is a short, very well written, concise book based on some 2,000 patients who underwent cardiac surgery and over 2,000 studies by cardiac catheterization. The book is designed to present radiologic findings in those forms of acquired and congenital heart disease with which the author had the most experience. There are chapters on mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency, rheumatic multivalvular lesions, atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary valvar stenosis, tetralogy of Fallot, and coarctation of the aorta.

Because this is a book relating to enormous personal experience, it omits areas in which the author had less experience, such as rare congenital heart lesions. Arteriosclerotic and hypertensive heart disease and certain other acquired lesions were not included because the author felt they did not lend themselves to the same type of analysis.

The book is well organized and well illustrated. Despite the fact that the author has great experience with selective angiocardiology, he chose not to use it extensively in this text because he feels there are ways of arriving at the diagnosis without its use. The entire stress of the book is to emphasize fluoroscopy and plain films. This approach has been tried in the past very often and has not been altogether successful because of lack of specificity. This new effort of getting away from studying the heart by selective contrast examinations probably will not be more successful than similar attempts in the past. The author, however, makes his points well. A scale of 6 is used for evaluating the enlargement of the heart and central vessels. Since this scale is not based on objective measurements, it attaches numerical values that can be somewhat deceptive.

The text is certainly worth perusal by everyone studying or practicing cardiac radiology. As it is not very detailed, however, it must be considered only as an excellent introduction to the subject.

ALEXANDER MARGOLIS, M.D.

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PSYCHOPATHOLOGY OF MENTAL DEVELOPMENT — Vol. XXIII, The Proceedings of the Fifty-Sixth Annual Meeting of the American Psychopathological Association held in New York City, February 1966—Edited by Joseph Zubin, Ph.D., Department of Mental Hygiene, State of New York; Department of Psychology, Columbia University, New York City; and George A. Jervis, M.D., Ph.D., Director, Institute for Basic Research in Mental Retardation, New York State Department of Mental Hygiene. Grune and Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1968. 658 pages, \$22.00.

This is a well-edited volume consisting of papers by numerous distinguished authors stressing a multiple discipline approach to the understanding of mental development and treatment of its psychopathology.

"The field of mental development has undergone a revolution in recent years. In the first decade of this century, work in this area dealt largely with intellectual development. The static model of intelligence promulgated by the early workers in this field has been replaced by a dynamic approach involving the interaction of social-cultural, hereditary, developmental, internal environmental, and brain-function models. The epidemiological approach has unearthed much information regarding the environmental underlay of retarded mental development extending even into the intrauterine life, while discoveries in genetics have laid bare the source of many rare conditions leading to the end result of mental retardation. Because the way the organism can respond to interferences is rather limited, while the number of potential interfering agents is almost infinite, the causes of mental retardation present a tangled skein which will require much effort and time to unravel." (From the Preface.)

The volume, which adequately represents each of the proposed scientific models, is divided into six major sections, as follows: Genetics and Neurophysiology; Social, Cultural and Perinatal Factors; Epidemiology; Behavioral Characteristics in Learning; Observational Techniques and Measurement of Intelligence; and Diagnosis and Rehabilitation. At the end of each of these sections, the papers which have been presented are discussed by

various members of the symposium which itself presents dynamic reading.

This reviewer was impressed that the editors have compressed an amazing amount of authoritative material into this comprehensive volume. It should prove to be a useful resource book for anyone working in a field having to do with mental development and mental retardation.

C. M. BINGER, M.D.

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PATHOLOGY OF LEUKEMIA — George D. Amromin, M.D., F.A.C.P., Chairman, Department of Pathology, City of Hope Medical Center, Duarte, California. Hoebner Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York, N. Y. (10016), 1968. 460 pages, \$26.50.

This book contains a comprehensive study of leukemia by a pathologist who has had a wide experience in this field. There are authoritative contributions on the electron microscopy of normal and leukemic cells by Dr. Kakefuda, on histochemical enzymology of leukemic cells by Dr. Melnick and of cytogenetics by Dr. Teplitz. As far as this reviewer is aware, this book is unique in its field.

The effects of leukemia on virtually every system of the body are described and emphasis is placed on the modifications of disease produced by modern chemotherapy. In general, the book is clearly written and there are very few printing errors. A few changes such as the Pseudo-Pelger cell and the Rieder cell are illustrated but not explained very clearly. In the electron microscopic sections, some of the methods are a little unusual; for instance, after fixation, tissue is placed in 25% alcohol or acetone and only then into higher concentrations. As far as staining for electron microscopy is concerned, a lead uranyl acetate stain is recommended rather than the more usual uranyl acetate-lead combination.

The illustrations of the light microscopic changes are adequate but not outstanding. The illustrations of electron microscopy are good; those of the histochemical changes are fair.

In view of its uniqueness, this book is highly recommended to pathologists because of its comprehensive coverage of the field and of its complications. The price is rather high, even though the book does not contain any color illustrations.

BORIS H. RUEBNER, M.D.

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AMBULATORY PEDIATRICS—Edited by Morris Green, M.D., Professor and Chairman, Department of Pediatrics, Indiana University School of Medicine; Physician-in-Chief, James Whitcomb Riley Hospital for Children, Indianapolis, Indiana; and Robert J. Haggerty, M.D., Professor and Chairman, Department of Pediatrics, University of Rochester, School of Medicine and Dentistry; Pediatrician-in-Chief, Strong Memorial Hospital, Rochester, New York. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 970 pages, \$22.50.

This important new book, which is concerned with the total problem of keeping the child well, of recognizing and coping with his developmental and behavioral problems, and of aiding the child, along with his family, in adjusting to minor and major health problems outside the hospital environment, is indeed timely, and helps fill a large void in pediatric education.

Doctors Haggerty and Green should be commended in their editing of this book, which reveals their considerable skill and experience in the field of ambulatory pediatrics. They have succeeded in compiling in a most readable and enjoyable manner the thoughts of a large number of authors who have an interest in this important and growing area.

The book is divided into eight major areas for quick

and easy orientation. It covers such diversified areas as the use of the telephone in pediatric practice and appointment systems to the treatment of juvenile rheumatoid arthritis and diabetes mellitus. Virtually all important areas involved in the care of the ambulatory pediatric patient are dealt with in a concise and practical manner.

This text is especially recommended to every pediatric resident, medical student, and also those in general practice who have pediatric patients.

GERALDINE DYER, M.D.

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FUNDAMENTALS OF PSYCHIATRY — Second Edition — Ian Gregory, M.D., Professor and Chairman, Department of Psychiatry, Ohio State University College of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 647 pages, \$13.00.

This Second Edition of *Fundamentals of Psychiatry* represents a radical revision of the First Edition published seven years ago. There are many tables, figures, and case histories added that contribute greatly to the book's clarity, presentation, and readability.

A feature unusual for most textbooks of psychiatry is a chapter on "The Analysis of Causation" that is helpful as a background to understanding the complexities of human behavior and the conflicting and contradictory literature on the etiology of psychiatric disorders. This is followed by excellent reviews of hereditary, other biological, psychological, and sociocultural, factors in the etiology of psychiatric disorders.

Dr. Gregory has called upon experts in certain fields for special topics. Brief descriptions of commonly used psychological tests are contained in a chapter by Philip A. Marks and John O. Kangas; a chapter on somatic treatments in psychiatry by Dr. B. C. Schiele includes an excellent section on drugs in current use; Dr. Charles A. Roberts contributed the chapter on preventive psychiatry; and Dr. Dean Coddington the chapter on disorders of childhood.

The theoretical orientation is "eclectic, holistic, and pragmatic." The book is intended for use by medical students and physicians and is recommended for its interesting and fresh approach that clearly reflect the author's thinking rather than just a systematic presentation of clinical syndromes.

NORMAN Q. BRILL, M.D.

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THE OSCILLOMETRIC VECTOCARDIOGRAM—Ralph M. Tandowsky, M.D., F.A.C.P., F.A.C.C., Fellow, Council on Clinical Cardiology, American Heart Association; Associate Clinical Professor of Medicine, Loma Linda University, Loma Linda, Calif.; With the Mathematical and Electronic Participation of William L. Morris, Ph.D., Chief Project Engineer, North American Aviation, Inc. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Ill., 1968. 339 pages, \$30.00.

To a rapidly expanding bibliography in vectocardiography this book is a useful addition. Its encyclopedic 339 pages are replete with actual VCG reproductions which tend to justify its rather expensive price.

The author is to be congratulated for presenting his experiences and concepts not in terms of an experimental or exotic lead system used by a few, but as related to the ubiquitous Frank System which, despite its theoretic faults, is certainly the most widely employed by those likely to be interested in this book. Similar laudable pragmatism is seen in the description of the Hart oscilloscope, the instrumentation with which many readers will be most familiar.

The first third of the book is devoted to the history of

vectocardiography, anatomic and physiologic review of cardiac function, and a detailed mathematic justification of technique which many beginners might feel is too explicit.

After a chapter on the normal vectocardiogram, there follow in order chapters on ventricular hypertrophy, heart block (including peri-infarction block and Wolff-Parkinson-White syndrome), chronic coronary disease including specific types of myocardial infarction, pericarditis, congenital heart disease and pulmonary heart disease. Of particular value to the practicing vectocardiographer are subsections on pectus excavatum, on conditions often confused with myocardial infarction, and on the vectocardiogram in and after exercise. The book concludes with an unknown practice review.

Although comprehensive the style and format of this book suggest the author intends it as a primer of vectocardiography. If this is so, certain editorial changes could render it more effective as an instructional tool. In an area where visual conception is all important, the written word *must* be visually associated with appropriate illustration. Unfortunately the publisher has seen fit to separate widely text, illustration and legend so that the reader must constantly flip from section to section on the same subject. Certain ambiguity in the text could also be eliminated by correcting some confusing typographical errors and by some editorial tightening of expression.

In all, there is a wealth of material present to the cardiologist willing to extract it.

ARTHUR D. SILK, M.D.

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CURRENT PSYCHIATRIC THERAPIES, Vol. 8—1968—Edited by Jules H. Masserman, M.D., Professor and Co-chairman of Psychiatry, Northwestern University, Chicago, Illinois. Grune and Stratton, Inc., 381 Park Avenue South, New York, N. Y. (10016), 1968. 258 pages, \$13.75.

Current Psychiatric Therapies consists of 33 articles by different authors on many subjects that vary from the use of dreams in promoting communication with parents in child psychiatry to a description of the organization and character of Soviet Psychiatry.

Beginning with an excellent introduction by Dr. Lawrence C. Kolb on the subject of psychiatric consultation and the infrequency with which it occurs between psychiatrists despite the frequency with which it is indicated, there are presentations on the occurrence of a smaller amount of social bias in the treatment of children, as compared with adults; on variations in therapeutic approaches such as one patient alternately seeing two therapists (a male and a female) concomitantly or two related patients seeing one therapist concomitantly but not together; on existential techniques, management of suicidal patients and on the treatment of dental disorders of psychogenic origin (that is primarily a condensed psychoanalytic explanation of an aspect of the problem).

There are articles on the treatment of the suicidal patient, of obesity, frigidity, alcoholism, as well as on the use of LSD in psychiatric therapy, the treatment of untoward LSD reactions, and lithium carbonate in manic-depressive states.

Developments in family psychotherapy are reviewed by Dr. Nathan Ackerman, a recognized pioneer in the field. Also included are contributions on family therapy of alcoholism and multiple family therapy.

There are articles on group therapy for married couples, for sex offenders, for the socially disadvantaged, marathon group therapy, making moving pictures as a form of group therapy and on group therapy training for psy-

chiatric residents and psychoanalytic therapy of aggression in groups.

Reports are also included on the prevention of hospitalization for the geriatric mentally ill, on gradients of hospitalization, organization and techniques of public school consultation, education for practice in the therapeutic community, and the role of the liaison psychiatrist.

The book is not intended to be a source document for the physician who is interested in learning the basic facts and techniques of psychiatric treatment but rather for those who wish to keep abreast of new approaches to, and experimental methods of, treatment of the mentally and emotionally ill.

NORMAN Q. BRILL, M.D.

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EUGENE WOLFF'S ANATOMY OF THE EYE AND ORBIT—Including the Central Connections, Development, and Comparative Anatomy of the Visual Apparatus—Sixth Edition—Revised by R. J. Last, M.B., B.S. (Adelaide), F.R.C.S. (Eng.), Professor of Applied Anatomy and Warden, Royal College of Surgeons of England. W. B. Saunders Company, 600 West Washington Square, Philadelphia, Pa. (19105), 1968. 529 pages with 465 illustrations, including 56 in color, \$19.00.

Mr. Last has brought this well-known textbook up to date. He has included in detail the latest work on electron microscopy including the scanning electron microscope. In spite of countless alterations and additions, the original pattern and character of Wolff's own work has been retained. This book is a must for every reference library.

R. M. SINSKEY, M.D.

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NEPHROLOGY—Volumes I and II—Jean Hamburger, G. Richet, J. Crosnier, J. L. Funck-Brentano, B. Antoine, H. Ducrot, J. P. Mery and H. De Montera. With the collaboration of P. Royer in the chapters on pediatrics. Translated by Anthony Walsh, F.R.C.S.I., Urologist, Jervis Street Hospital, Dublin. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. Volume I, pp. 1 through 709; Volume II, pp. 710 through 1312. Price: \$50.00 the set.

The two volume set on Nephrology by Hamburger and eight other authors (translated from the French edition) is extremely well written and very lucid. The authors have devoted a large portion of the volumes to renal physiology, symptomatology of renal disease, and renal function tests. These are very basic to the understanding of clinical nephrology; and, therefore, I feel that it is extremely worthwhile for the parts on the introduction to clinical nephrology to be as inclusive as they are.

The next section deals with some of the major problem areas in renal disease such as the nephrotic syndrome, renal failure, and hypertension of renal origin, etc. Considerable effort has been devoted to a discussion of the basic underlying pathophysiology as it relates to each of these conditions. This provides an excellent background to understand the basic defect and rationale of treatment.

Following this portion, the book is divided into large major classifications with subclassifications to deal with specific disease entities or specific problems which primarily affect the kidney. Each of these subheadings are discussed as specific entities, some in considerable depth and others quite superficially. Many of the subheadings treated in this book have not been covered in any of the other popular textbooks of nephrology. They are an excellent source of reference material for specific patient problems. In these sections, also, the authors devote considerable space to pathologic physiology judiciously. This helps to make the textbook a great deal more interesting and understandable.

The table of contents in the front of each volume is extensive so that there is very little difficulty in finding a specific topic. Also, the volumes are well indexed in the back of each volume. Each section has a rather extensive bibliography which is excellent for reference material. The authors quote rather widely, particularly from the European literature as well as from some of the major American journals. The most recent references go up to 1964.

In summary, I think this is an excellent book that is well written and covers essentially all of the subjects in the field of renal disease. It would be a very good reference book for nephrologists or reference material on renal diseases for a large medical service or medical group.

STEWART SHANKEL, M.D.

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THE PSYCHIATRIC CONSULTATION—Werner M. Mendel, M.D., Professor of Psychiatry, University of Southern California School of Medicine, Los Angeles, California, and Philip Solomon, M.D., Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 221 pages, \$9.75.

The editors of this volume note that the growing interest of the public in psychiatry, together with recent social legislation making it possible for the lower economic groups to receive psychiatric care for conditions other than psychosis, is placing a tremendous burden on the mental health manpower pool. They suggest that as psychiatric training centers cannot possibly train enough psychiatric specialists to serve the treatment and prevention needs of the population, the emphasis must be on the psychiatrist as the leader of a mental health treatment team and as a consultant to the non-psychiatrist physician and others in the helping disciplines. Dr. Solomon considers the symposium on which this book is based to be "the first substantial and nationwide recognition of the importance of the general field of consultation in psychiatry."

The objective of the book is to define the process of consultation, evaluate techniques of teaching consultation, and present some specialized techniques of consultation in various fields. Dr. Mendel notes that most educators in the field of psychiatry agree on a model of the ideal consultation but recognize the great disparity between this model and actual consultation practice (a situation that undoubtedly exists in other medical specialties, as well). The difference between model and practice is attributed to the present lack of interest and research emphasis in this aspect of psychiatry. Dr. Henry Brosin lists a series of common complaints made by medical colleagues that psychiatrists should seriously consider. Whether or not they are based entirely on fact, they do reflect the image that some psychiatrists project and that can influence the effectiveness of the psychiatrist as a consultant.

The first section of the book deals with teaching the consultation process, and emphasizes that variations in teaching techniques occur for the most part in connection with the different levels of consultation—patient centered, colleague centered, and agency centered. The second, and larger, part of the book deals with special techniques and situations in which the psychiatric consultation takes place—a county general hospital, a community agency, schools and colleges, government agencies, courts, family counseling services, the clergy, and industry. The list is not exhaustive but could be expanded to include prisons, poverty programs, emergency clinics, alcohol and drug abuse clinics, housing and resettlement agencies, and many more.

With 18 articles by contributors with differing points of view, this volume suffers from the usual shortcomings of such a presentation—duplication, lack of continuity of theme, and a disjointed quality. It does, however, as the editors intended, represent a beginning in the structuring and systematizing of a new discipline. The expansion of psychiatry to touch nearly every area of human activity has taken place over a long period without formal teaching or organization of its consultation aspects. This book discusses many of the basic principles, but as with any clinical subject, the content can be no substitute for clinical practice under the supervision of an expert. It is in the clinical situation that one learns.

ALEXANDER SIMON, M.D.

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ORTHOPEDIC DISEASES—Physiology, Pathology, Radiology—Third Edition—Ernest Aegerter, M.D., Professor of Pathology and Director of the Department of Pathology, Temple University Health Sciences Center; Professor of Orthopedic Pathology, University of Pennsylvania Graduate School of Medicine; Chief in Pathology, Philadelphia General Hospital; Consultant in Pathology, Frankford Hospital, United States Naval Hospital, Veterans Administration Hospital, Shriner's Hospital for Crippled Children, Philadelphia; Pennsylvania State Hospital for Crippled Children, Elizabethtown, Pennsylvania; the A. I. duPont Institute, Wilmington, Delaware; and John A. Kirkpatrick, Jr., M.D., Radiologist, St. Christopher's Hospital for Children; Professor of Radiology, Temple University Health Sciences Center; Radiologist, Children's Heart Hospital; Attending (Radiology), Veterans Administration Hospital, Philadelphia. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 906 pages, \$23.00.

This third edition of *Orthopedic Diseases*, by Aegerter & Kirkpatrick represents a further enlargement and improvement of their previous excellent text. The first five chapters are an excellent and logical presentation of the basic material of histology, embryology, physiology, and the interpretation of roentgenograms.

In each of the following sections a logical presentation of the disease entity is made, with first a description of the entity, followed by roentgenographic manifestations, with excellent reproductions of the roentgenograms, the description of the pathologic morphology, accompanied by clear reproductions of the photomicrographs, and finally, a discussion of the prognosis.

The material covered in this portion of the book is: first, disturbances of skeletal development and disturbances in the normally formed skeleton; tumors and tumor-like processes; and finally, diseases of joints and muscles and soft-part tumors.

I find this book to be excellent for medical students to give them a clear and concise picture of this type of orthopedic problem. It should be in the library of every orthopedic resident and every practicing orthopedic surgeon.

CHARLES BECHTOL, M.D.

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TEXTBOOK OF OTOLARYNGOLOGY—Third Edition—David D. DeWeese, M.D., Professor and Chairman of the Department of Otolaryngology, University of Oregon Medical School, Portland, Oregon, and William H. Saunders, M.D., Professor and Chairman of the Department of Otolaryngology, The Ohio State University College of Medicine, Columbus, Ohio. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 457 pages, \$11.50.

Intended primarily for the medical student and the general practitioner, the first edition of this book was very well received. It was published in 1960 when the existing texts had gone through many inadequately revised editions. The third edition of DeWeese and Saunders suffers from the same deficiencies as the texts its first edition was intended to replace.

Although the design and color of the cover are new, the titles, number and order of the chapters are identical with those of the first edition. None of the chapters has been extensively rewritten. A small number of illustrations have been replaced or deleted; several new ones have been added. The most extensive changes are in Chapter 6, in which the new laryngeal illustrations are a significant improvement, and in Chapter 9, to which four charts covering tracheotomy care have been added. A section of mediastinoscopy, consisting of one short paragraph, one illustration, and one reference, has been added to Chapter 10. A few additional references have been added to the bibliographies at the ends of some of the chapters.

Despite the inadequacy of the changes, we are indebted to Dr. DeWeese and to Dr. Saunders for providing us with the best available American otolaryngology text for medical students and general practitioners. Current owners of editions one or two need not replace them. Anyone seeking a good, basic otolaryngology text would do well to consider the new edition of DeWeese and Saunders. It is the hope of the reviewer that the fourth edition will be adequately revised.

CHARLES P. LEBE, M.D.

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PEDIATRIC THERAPY—Third Edition—Harry C. Shirkey, B.S. (Pharm.), M.D., F.A.A.P. (Editor), Director, The Children's Hospital of Birmingham, Alabama; Professor and Director, Division of Clinical Pharmacology, Department of Pediatrics, and Associate Professor, Department of Pharmacology, Medical College of Alabama, Birmingham, Alabama; Professor and Chairman, Department of Pharmacology, Samford University, Birmingham, Alabama; Member, Revision Committee, and Chairman, Pediatric Panel, Pharmacopeia of the United States. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 1294 pages, \$25.00.

Almost any physician who treats children needs a textbook devoted exclusively to pediatric therapy. Currently two such books are available. One of these, *Pediatric Therapy*, Harry Shirkey, editor, is now in its third edition. The book is divided into the traditional categorical arrangements of diseases (respiratory system, blood, genitourinary system, etc.), and the principles and all practical details of a complete therapeutic regimen are set forth. In addition, there are more general chapters which deal with drug treatment, drug reactions, treatment of symptoms, etc., an extensive table of poisons and their treatments, and a very extensive table of recommended drugs and dosages. Since there are 89 contributing authors, it is not surprising that the end result is a bit uneven in quality; however, most of them succeed in presenting a practical and complete approach to the delivery of care to sick children. The presentations benefit from very liberal use of illustrative figures and lists of pertinent references.

Since the decision for most physicians who treat children will not be whether to buy such a book but, rather, which one should be bought, some comparison with its main competitor, *Current Pediatric Therapy*, Drs. S. S. Gellis and B. Kagan, editors, seems appropriate. In general, these books are similar, with a few distinct differences. The Gellis-Kagan book deals solely with specific disease entities and lacks the extensive discussions of general care given in the first section of the Shirkey book, and also does not make use of illustrative figures. On the whole, the Gellis-Kagan book is more scholarly in its approach to specific diseases, while the Shirkey book places more emphasis on the practical details of total patient care.

If one has the second edition of the Shirkey book,

enough new information is not offered in the third edition to justify its purchase. However, compared to the first edition, there are enough new and/or significantly revised chapters so that it could be replaced with the third.

RODERIC H. PHIBBS, M.D.

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MONOCLONAL AND POLYCLONAL HYPERGAMMAGLOBULINEMIA—Clinical and Biological Significance—Jan Gösta Waldenström, Head of the Department of Medicine in Malmö at the University of Lund. Vanderbilt University Press, Nashville, Tenn. (37203), 1968. 223 pages, \$6.95.

This book is a compact exposition of the disorders of immunoglobulins by a most distinguished clinician. As in most of his publications, it is written in an informal, chatty style, in which he allows access to his thoughts, most of which are born out of long and extensive clinical experience. Throughout the book, the author leans heavily on this experience and presents a large amount of case material. Although he constantly refers to the available literature, it is his data which shapes his thinking. This is probably the book's greatest strength. It is also probably its weakness in that a large body of clinical material on these disorders from other centers is summarized only briefly.

The book covers the following materials. The nomenclature of the gamma globulins; the nature of (M) components and so called paraproteins; the clinical importance of monoclonal vs. polyclonal hypergammaglobulinemias; the diagnostic importance of the estimated sedimentation rate; the incidence of the monoclonal disorders of multiple myeloma macroglobulinemia, etc.; some discussion of the metabolic problems of these disorders; a brief section on cryoglobulins; an important discussion of monoclonal essential hypergammaglobulinemia and material on polyclonal hypergammaglobulinemias including autoimmune diseases, purpura hypergammaglobulinemia, circulating anticoagulants and sarcoid like disease. The book ends with a section on the etiology and metabolic aspects of monoclonal disease which includes some of the author's thoughts on malignant disease in general.

The chapter on the nomenclature is somewhat out of date and the new information on IgG subclasses is not included. Further, the current concepts of heavy chain disease i.e., proteins which are more than just a Fc fragment and are probably heavy chains with large areas of Fd fragment deletion were not available at the time of his writing. The author's discussion of the term paraprotein and the evidence for and against it are timely. He favors the concept that M components are antibody molecules which we must find the antigen. He devotes an entire chapter to the problem of incidence and etiology of these disorders. This information has been unavailable (in the form presented) and as such is worthy of the reader's attention. The chapter on metabolic problems was disappointing in that no discussion of the role of the kidney in the catabolism of gammaglobulin and Bence Jones proteins was included. This is an important subject which has direct bearing on the etiology of myeloma renal disease. The discussion on hypercalcemia, however, is more to the point and raises the question of the presence of a calcium mobilizing factor in these patients.

The information provided about a monoclonal essential hypergammaglobulinemia as a clinical problem is important in this day. The availability of potent drugs which, when indiscriminately used on patients who have not had myeloma, can cause severe and fatal iatrogenic disease. The existence of, and criteria for, diagnosis of

benign vs. early myeloma are discussed. The author leans heavily on maintenance of a stable level of gamma-globulin for diagnosis of benign disease. The book includes discussions on the concept of autoimmune diseases, the entity of purpura hyperagglutininemia and malignant disease in general. The latter subject is again treated anecdotically and as such is more interesting for its speculations than for its hard data.

The book is of interest primarily to internists and those physicians who see numbers of patients with malignant disorders. It is worth reading particularly for the enjoyment of traveling through the years of observation and thinking of this monumental physician.

MALCOLM R. MACKENZIE, M.D.

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PHYSIOLOGICAL PRINCIPLES OF GASTRIC SURGERY—Harry A. Oberhelman, Jr., M.D., Professor of Surgery, Stanford University School of Medicine, Palo Alto, California. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Ill. (62703), 1968. 95 pages, \$7.50.

The author has presented a timely and up-to-date monograph, setting forth the physiological principles upon which gastric surgery is based. He has brought together the important contributions in gastric physiology and presented them to the reader in a clear and concise way. Dr. Oberhelman is uniquely qualified to this because of his long interest and personal contributions, clinically and in the laboratory, to this field. This book begins with an excellent anatomical description of the stomach depicting its innervation, histological characteristics, and circulation. The second chapter succinctly covers the basic physiology of gastric secretion, digestion, and motility. The material presented in the first two chapters provides the foundation and the physiological basis for the ensuing chapters which discuss the surgical management of the duodenal ulcer, gastric ulcer, stomal ulcer, and peptic ulceration associated with extra-gastric factors. The chapter entitled "Physiological Principles of Complications of Gastric Surgery" is exceedingly well done and presents to the student and physician an excellent discussion of the pathogenesis of the complications of gastric operations, and details as to how they may be prevented or treated. The final chapter discusses the pathophysiology and therapy of peptic esophagitis.

The author is to be complimented for condensing a vast amount of information and presenting it in a lucid, easy-to-read manner. This text is comprehensive, very well organized, and serves to relate clinical practice to its basic science origins. In dealing with peptic ulceration the author continually emphasizes the underlying pathophysiology and associates this with diagnostic and therapeutic regimens. This book should appropriately find its place in every medical school library and is particularly recommended for every medical student, resident, surgeon or physician interested in medical or surgical gastroenterology.

EARL F. WOLFMAN JR., M.D.

* * *

THE RADIOBIOLOGY OF HUMAN CANCER RADIOTHERAPY—J. Robert Andrews, M.D., D.Sc. (Med.), Professor of Radiology and Director of Radiotherapy, Georgetown University Medical Center; Chief, Radiotherapy Section, Radiology Service, Washington Veterans Administration Hospital; Consultant: Clinical Center, National Institutes of Health; District of Columbia General Hospital; Providence Hospital; Sibley Memorial Hospital; formerly: Chief, Radiation Branch, National Cancer Institute, National Institutes of Health; Professor and Director of Radiology, Bowman Gray School of Medicine and North Carolina Baptist Hospitals.

W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 271 pages, \$19.00.

The major effort of this book on radiobiology is to present the author's own experience or his investigations or from his evaluation of the experiences and the results of others in this field.

Often books are written largely by a number of contributors responsible for specific areas. This book was largely the author's effort and he had the benefit of collaboration with those who have assisted in his investigations or who were afforded an opportunity to analyze his results.

On page 4 in the discussion of electronic equilibrium the context of the quote from Williams, 1966, is inadequate. On page 7 the statement is made that "Mammalian cells are killed by ionizing radiations with a probability which is the reciprocal of the probability of their survival; that is, if the probability of killing is, say, 80 percent then the probability of survival is 20 percent." The reciprocal of 80 percent is 125 percent rather than 20 percent.

The author has had considerable experience in the field of radiobiology and radiation therapy and he has given a great deal of thought to the presentation of this material which is well organized.

The book is recommended for reference for radiobiologists and for practicing radiation therapists. An excellent bibliography is included.

JUSTIN J. STEIN, M.D.

* * *

PRINCIPLES AND PROBLEMS OF ISCHEMIC HEART DISEASE—Tinsley Randolph Harrison, M.D., Professor of Medicine, College of Medicine, University of Alabama; Distinguished Professor, University of Alabama; Attending Physician, University Hospital, Birmingham, Alabama; and T. Joseph Reeves, M.D., Professor of Medicine, Alabama Heart Research Professor, Associate Professor of Physiology, Director, Cardiovascular Research and Training Program, College of Medicine, University of Alabama. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. (60601), 1968. 474 pages, \$20.00.

This book is a valuable asset to the working library of the internist. There is no padding, no trivia; the bibliographies for each chapter are as they should be—selective. The literary style is elegant, with tasteful allusions to the classics of medicine and mythology. This book is novel in that it is not solely disease-oriented, but from its first page assigns more importance to the patient than to the heart. A number of conversations between hypothetical physicians and imaginary patients gives to the reader a sense of taking a residency in ischemic heart disease (IHD) from the the authors. In the appendix are copies of actual instructions given to 20 different patients, from "a healthy man considered a likely candidate for coronary disease," a woman plagued with hyperventilation, sufferers from various degrees of angina pectoris, and the victim of acute myocardial infarction.

Case 21, Subjective Aspects of an Acute Myocardial Infarction (as related by the patient), describes the heart attack that struck Dr. Harrison as this book was nearing completion after three years of work. Said this patient, "During the uneventful illness, and after recovery from it, the book was almost completely re-written. There are many small details that are important to patients, but are often overlooked by physicians and that had been largely neglected in our initial draft. These have now been inserted."

Hence, the reader is not astonished to find that the opening chapter deals with The Problem of Fear. Following Some Definitions and Explanations is Highlights in

the History of Ischemic Heart Disease. In only six pages is distilled our knowledge of IHD from Hippocrates to Frank Wilson.

Part two encompasses Some Etiologic and Epidemiologic Considerations. Methods of Examination come in for a lucid evaluation, in which the importance of eliciting a detailed history from the patient is constantly emphasized. Part four deals with Physiology and Pathophysiology. Part five discusses Some General Aspects of Prevention and Treatment. The postulation of atherogenesis vs. thrombogenesis as the basic mechanism in myocardial infarction is thoughtfully presented. The debate about oral anticoagulants for short or long periods and coumarin vs. heparin is reported sans prejudice. Part six is devoted to Angina Pectoris.

In 73 pages, Harrison concentrates his years of experience with the diagnosis of chest-pain. This section alone is worth the price of the book and will be a *vade mecum* when a patient with obscure chest-pain makes his appearance. A chapter on Myocardial Infarction logically follows, introduced by appropriate Historical Landmarks. Problems of Faints and Spells is explored in 13 pages of wisdom. The uncertainties of prognosis precedes the Surgical Treatment of IHD. Wondrous to read is the last chapter, Management of Apprehension.

This is a very personal book in that it reflects the authors' personal experience with IHD patients. Fact is neatly distinguished from hypothesis by printing the latter in smaller type. When the authors have had no experience with a drug, they say so, as in the case of furosemide (p. 395). Since this is a highly personal book, the authors' opinions are not disguised. In angina of mitral stenosis, Paul Wood's concept is ignored. Although the section dealing with precordial movements is exceptionally complete, the importance of the pulmonic closure sound is neglected (p. 383). The efficient Holter monitor for catching suspected arrhythmias is not used (p. 176, 411). In the prognosis of acute myocardial infarction, the peak of SGOT elevation is disregarded (p. 424). That complete heart block can appear intermittently despite a normal PR interval as a cause of faints and spells is not mentioned (Arch. Gen. Psychiat. 18: 112, 1968). The criteria for the diagnosis of ventricular tachycardia are very loose (p. 175). Lipoprotein-typing is not discussed.

A few errors merit correction in a new printing. In Table 5-2, the blood pressure in coarctation of the aorta is said to be "high in the legs, low in the arms." Methoxamine is advised in the text for the drug-tray, but is not listed in Table 20-2. In this same table, the dose of isoproterenol is lacking mgm after the numerals. The directions in the Appendix are for patient 19 not patient 9 (p. 408). Death from crucifixion is said to be caused by postural hypotension; Burch makes a better case for respiratory failure. Optical is printed instead of optional (p. 430).

This evaluation might have been guessed from the names on the title-page. The late Alfred Blalock named as his life's major beneficent influence Tinsley Harrison (while they were both at Vanderbilt). The *Principles of Internal Medicine*, conceived by Harrison, made obsolete the smorgasbord-type textbook of medicine and pushed teaching from the podium to the bedside.

EDWARD SHAPIRO, M.D.

* * *

A TECHNIQUE FOR EXTRACORPOREAL CIRCULATION—Raymond C. Stofer, D.V.M., In charge of extracorporeal circulation for the Norman E. Shumway Heart Surgery Team; Research Associate, Division of Cardiovascular Surgery, Stanford University School of Medicine, Palo Alto, California. Foreword by Norman Shumway, M.D., Chief, Division of Cardiovascular Surgery, Professor of Surgery, Stanford University School of Medicine, Palo

Alto, California. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1968. 115 pages, \$6.75.

This monograph, written as a primer in the preparation and assembly of heart-lung equipment and in the conduction of extracorporeal circulation, will be of interest to both the neophyte heart-lung and experienced bypass technician. Although didactic in its content and often cookbook in its format, the book portrays both graphically and interestingly the author's ten years' experience with cardiopulmonary bypass, his philosophy toward training of technicians, and exemplifies his personal devotion toward development of this technique into an art and a craft.

Chapters in this book include segments of extracorporeal circulation support procedures often forgotten in more major surveys of this field such as "What Can Go Wrong?", The Processing Technique of Equipment, and Suppliers of Custom Built Accessories.

The book is, therefore, recommended for those individuals concerned with either the training of cardiopulmonary technicians or operators of experience who wish to review the author's basic and applied approach to this often neglected segment of cardiac surgery.

EDWARD J. HURLEY, M.D.

* * *

THE CARE OF THE RHEUMATOID HAND—Second Edition—Adrian E. Flatt, M.A., M.D., F.R.C.S., F.A.C.S., Professor of Orthopedic Surgery, University of Iowa, Iowa City, Iowa; Hunterian Professor of Royal College of Surgeons of England; Civilian Consultant to U.S. Air Force in Hand Surgery; Past President, Midwestern Association of Plastic Surgeons. With Foreword by Russell L. Cecil, M.D. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 234 pages, \$14.00.

In new fields of surgery changes often occur quite rapidly and when the information is published in book form, an early revision bringing the text up to date reflects the interest and devotion of the author to his subject. Such is the case in the *Care of the Rheumatoid Hand* by Dr. Flatt. Not only has the material in the previous edition been reviewed and updated but a new chapter has been added on the results of surgery for this condition.

Dr. Flatt has long been deeply interested and concerned in this problem and has been a leader in this work in this country. His text not only reflects and records his opinions and procedures but also incorporates that of importance from other investigators, not only here but in the major European clinics dealing with this subject. The text is carefully planned, well written, well illustrated, and divided in chapters to specifically cover the particular phases under consideration. The chapters on the general principles of care and on the nonoperative treatment are particularly significant to those who would undertake this type of surgery. The text is probably the most concise, and the best assessment of the care and the surgery of the rheumatoid hand that is available to date.

The publication of the results of the various types of surgery is highly commendable and enlightening.

Although this book is undoubtedly primarily designed for surgeons, it is to be highly recommended to internists and rheumatologists as well since these men are the ones to first see the beginning ravages of this most debilitating condition.

In reading the text through one cannot fail to recognize the important role that judicious surgery can play in all phases of rheumatoid arthritis as it affects the hands.

L. D. HOWARD, JR., M.D.

Emergency Heart Valve Replacement

EDWARD B. STINSON, M.D., AND NORMAN E. SHUMWAY, M.D., *Stanford*

■ *Sixteen patients with terminal cardiac failure due to valvular heart disease had emergency operation for valve replacement. Four patients did not survive, because of irreversible myocardial or secondary organ involvement. The remainder, however, had immediate reversal of heart failure after operation, and all became fully active following discharge. Recognition of refractory decompensation in valvular heart disease demands prompt consideration of surgical intervention.*

SUDDEN HEMODYNAMIC DETERIORATION may occur unpredictably in valvular heart disease. This is especially striking in cases of acute valvular insufficiency due to endocarditis. At such a point medical therapy may become ineffective and even dangerous in the presence of terminal low cardiac output state. This report presents our experience with 16 consecutive cases of emergency valve replacement performed at Stanford University Medical Center in the past two years and emphasizes the importance of prompt surgical intervention in salvage of these critically ill patients.

Criteria defining the emergency status of these patients are necessarily subjective, but generally include the following: rapidly progressive cardiac failure with critically low cardiac output by catheterization or clinical estimation, progressive central nervous system depression, acutely increasing prerenal azotemia, and frequently hepatic failure. Many other patients with chronic and advanced valvular heart disease who were operated on during this period of time fulfilled several of these criteria but are not included in this report because death was not considered imminent, and operation was scheduled less urgently.

Clinical Material

Sixteen patients are included and the clinical data are summarized in Table 1. Average age was 50.3 years, and six of the patients were 45 or younger. This reflects the severe hemodynamic consequences of combined aortic and mitral valve disease in two patients, ages 31 (Case 13) and 40 (Case 14), and of acute aortic insufficiency due to endocarditis in two patients, ages 25 (Case 9) and 45 (Case 10). Except for those with endocarditis, all patients had a history of known valvular heart disease with gradually worsening symptoms (extending over 20 years in one patient with mitral stenosis), culminating in rapidly progressive deterioration in the immediate preoperative period. In most patients no clearly identifiable precipitating factors were recognized, although pulmonary emboli, recurrent rheumatic activity or excessive diuresis were suggestive features.

Immediately preoperatively the clinical signs and symptoms of low cardiac output included to some degree in all patients weakness, air hunger, feeble pulses, hypotension, pale color, oliguria and mental obtundation. Pulmonary edema or severe pulmonary congestion was present in all, and variable atrial or ventricular arrhythmias were often prominent. Evidence of compromised perfusion included acutely rising blood urea nitrogen and serum bilirubin. In many patients signs of sys-

From the Division of Cardiovascular Surgery, Stanford University School of Medicine, Stanford.

Submitted 17 September 1968.

Reprint requests to: Division of Cardiovascular Surgery, Stanford University School of Medicine, Stanford 94305 (Dr. Shumway).

TABLE 1.—Clinical Data on 16 Patients Who Had Emergency Operation to Replace Cardiac Valve

Patient	Age Sex	Lesion	Clinical Status	EKG	Chest X-ray	Catheterization	Course	Follow-up
<i>Aortic Valve Replacement</i>								
1.	44 M	Calcific aortic stenosis.	Symptoms for 4 years with 3 weeks of progressive failure. Severe low cardiac output state. Obtunded. BUN 50 mg per 100 ml.	Sinus tachycardia. Left bundle branch block.	Cardiomegaly. Pulm. vasc. congestion. Pleural effusions.	None.	Tracheostomy. Uncomplicated recovery. Discharge on 18th postop. day.	Well and working at 6 mo.
2.	69 M	Calcific aortic stenosis.	Symptoms for 2 years with 1 month of progressive failure. Cachectic. Severe low c.o. state. Obtunded. BUN 55 mg per 100 ml.	NSR. 1° block. LAH. LVH.	Cardiomegaly. Pulm. vasc. congestion. Pleural effusions.	C.I. 1.5 1/m/M ² . LV 130/23 e.d. RV 54/9 e.d. Aortic valve area 0.37 sq cm.	Tracheostomy. Atrial fibrillation. Discharge on 19th postop. day.	Well at 6 mo.
3.	61 F	Calcific aortic stenosis.	Symptoms for 6 mos. with 2 weeks of progressive failure. Severe low c.o. state. Obtunded and delirious. BUN 35 mg per 100 ml.	Atrial fibrillation. LVH. IV conduction defect.	Cardiomegaly. Pulm. vasc. cong. Pulm. edema.	None.	Uncomplicated recovery. Discharge on 13th postop. day.	Well at 6 mo.
4.	64 M	Calcific aortic stenosis.	Symptoms for 6 mos. with 5 days of progressive failure. Severe low c.o. state. Obtunded. BUN 66 mg per 100 ml.	Sinus tachycardia. LAH. LVH.	Cardiomegaly. Pulm. vasc. cong. Pleural effusions.	None.	Atrial fibrillation, reverting to NSR. Discharge on 9th postop. day.	Well at 1 year.
5.	56 M	Calcific aortic stenosis.	Symptoms for 2 years with 1 month of progressive failure. Severe low c.o. state. Semicomatose. BUN 149 mg, bilirubin 6 mg per 100 ml.	Sinus tachycardia. 1° block. Left bundle branch block.	Cardiomegaly. Pulm. vasc. cong.	C.I. 1.2 1/m/M ² . LV 136/37 e.d. RV 68/12 e.d. Aortic valve area 0.34 sq cm.	Died of progressive hepato-renal failure on 5th postop. day.	
6.	63 M	Calcific aortic stenosis.	Symptoms for 4 years with 4 months of progressive failure. Severe low c.o. state. Digitoxic. Obtunded. BUN 69 mg per 100 ml.	Atrial fibrillation. Multifocal vpc's.	Cardiomegaly. Pulm. vasc. cong.	None.	Tracheostomy. Uncomplicated recovery. Discharge on 17th postop. day.	Re-op. 1 year postop. for periprosthetic leak—recovery.
7.	55 M	Calcific aortic stenosis.	Symptoms for 3 years with 1 month of progressive failure. Severe low c.o. state. Digitoxic. Obtunded. BUN 47 mg per 100 ml.	LAH. Left bundle branch block.	Cardiomegaly. Pulm. vasc. cong. Pleural effusions.	None.	Tracheostomy. Ventricular fibrillation 3rd postop. day. Discharge on 18th postop. day.	Well at 2 mo.
8.	53 M	Aortic insuff. (staph. aureus endocarditis).	Symptoms of CHF for 2 weeks with 5 days of rapidly progressive failure. Severe low c.o. state. Obtunded. Resolving hemiparesis. BUN 144 mg per 100 ml.	Sinus tachycardia. LAH. LVH.	Left ventricular enlargement. Pulm. edema. Left pleural effusion.	None.	Died of pneumonias and septicemia on 6th postop. day.	
9.	26 M	Aortic insuff. (anaerobic streptococcus endocarditis).	Symptoms of CHF for 3 months with 4 days of rapidly progressive failure. Severe low c.o. state. Obtunded. BUN 40 mg, bilirubin 2.6 mg per 100 ml.	Sinus tachycardia. LAH. ? LVH.	Cardiomegaly. Pulm. vasc. cong. Pleural effusions.	None.	Tracheostomy. Uncomplicated recovery with treatment for endocarditis. Discharge on 29th postop.	Well at 3 mo.

TABLE 1.—Clinical Data on 16 Patients Who Had Emergency Operation to Replace Cardiac Valve (Continued)

Patient	Age Sex	Lesion	Clinical Status	EKG	Chest X-ray	Catheterization	Course	Follow-up
10.	45 M	Aortic insuff. (endocarditis, ? organism).	Rapidly progressive failure for 2 weeks. Severe low c.o. state. Lethargic. BUN 26 mg per 100 ml.	Sinus tachycardia. 1° block. Right bundle branch block.	Cardiomegaly. Pulm. vasc. cong. Pleural effusions.	None.	Tracheostomy. Recurrent ven- tricular fibrilla- tion on 2nd and 14th postop. days. Discharge on 28th postop. day.	Mild residual CHF at 2 mo.
Mitral Valve Replacement								
11.	49 F	Mitral stenosis (rheumatic).	Symptoms for 15 months, with gradually progressive failure. Severe low c.o. state. Semicomatose. BUN 59 mg, bilirubin 2.9 mg per 100 ml.	Sinus tachycardia. PAT. Biatrial hypertrophy. RVH.	Cardiomegaly. Pulm. vasc. cong. Pulm. edema. Pleural effusions.	RV 109/22 e.d. PA 109/59. PAW 31 mean. C.I. 0.99 l/m/M ² .	Tracheostomy. Died on 13th postop. day of progressive myocardial failure.	
12.	40 M	Mitral insuff. (ischemic heart disease).	Symptoms for 1 year with 9 months of progressive failure. Severe low c.o. state. Semicomatose. BUN 25 mg per 100 ml.	Sinus tachycardia. 1° block, IV block. LAH.	Cardiomegaly. Pulm. vasc. cong. Left pleural effusion.	None.	Expired in O.R. (myocardial failure)	
Aortic and Mitral Valve Replacement								
13.	31 M	Aortic and mitral stenosis and insuff.	Symptoms for 1 year with 2 weeks of progressive fail- ure. Severe low c.o. state. Obtunded. BUN 33 mg per 100 ml.	Atrial fibrillation. LVH.	Cardiomegaly. Pulm. vasc. cong. Pulm. edema. Pleural effusions.	None.	Tracheostomy. Uncomplicated recovery. Dis- charge on 19th postop. day.	Well at 9 mo.
14.	40 F	Aortic stenosis and insuff., mitral sten.	Symptoms for 20 years with 2 weeks of rapidly pro- gressive failure. Severe low c.o. state. Obtunded. BUN 97 mg, bilirubin 5.5 mg per 100 ml.	Atrial fibrillation.	Cardiomegaly. Pulm. vasc. cong. Right pleural effusion.	RV 110/31 e.d. LV 231/32 e.d. C.I. 0.8 l/m/M ² .	Tracheostomy. Uncomplicated recovery. Dis- charge on 19th postop. day.	Well at 5 mo.
Post-prostheses.								
15.	68 F	Periprosthetic mitral leak.	6 weeks postop. 7 days of rapidly progressive failure. Severe low c.o. state. Ob- tunded. BUN 32 mg per 100 ml.	Atrial fibrillation. LVH.	Cardiomegaly. Pulm. vasc. cong. Pleural effusions.	None.	Tracheostomy. Uncomplicated recovery.	Well at 10 mo.
16.	40 F	Periprosthetic mitral leak (? endo- carditis).	5 months postop. Acute failure. Severe low c.o. state. Semicomatose. BUN 15 mg per 100 ml.	Atrial fibrillation. Incomplete right bundle branch block.	Cardiomegaly. Pulm. edema.	None.	Tracheostomy. Uncomplicated recovery with treatment for endocarditis. Discharge on 32nd postop. day.	Well at 6 mo.

LEGEND: BUN=blood urea nitrogen, C.O.=cardiac output, NSR=normal sinus rhythm, LAH=left atrial hypertrophy, LVH=left ventricular hypertrophy, RVH=right ventricular hypertrophy, IV=intra ventricular, VPC=ventricular premature contraction, C.I.=cardiac index, LV=left ventricle, RV=right ventricle, e.d.=end diastolic, PA=pulmonary artery, PAW=pulmonary artery wedge. All pressures in mm of mercury.

temic congestion were absent or minimal because of vigorous preoperative diuresis.

Only four patients had preoperative cardiac catheterization. In these patients (Cases 2, 5, 11, 14) critically reduced cardiac indices of 1.5, 1.2, 0.99, and 0.8 liters per minute per square meter of body surface were found. In the remainder the clinical condition was deemed too precarious to permit hemodynamic study, and clinical signs and history were sufficiently definitive to justify operative intervention.

Operative management was concentrated on the rapid institution of cardiopulmonary by-pass following the induction of light general anesthesia supplemented with muscle relaxants. In all cases standard cardiopulmonary by-pass techniques using a disc oxygenator with flows of 40 to 60 ml/kg/min under mild hypothermia were employed. Whole blood was used as the preferred priming solution in 13 patients, but in three Hartmann's solution was satisfactorily substituted. Despite the desperate cardiopulmonary status of all of these patients, in only one did cardiac arrest occur under general anesthesia and in this case the circulation was successfully supported manually until by-pass was effected.

Valve replacement was performed in all patients, using a Starr-Edwards prosthetic valve in 15 cases and an aortic homograft for aortic substitution in one (Case 1). Elective tracheostomy was utilized in 12 patients because of advanced pulmonary congestion and edema and seriously debilitated clinical state. One operative death occurred, in a 40-year-old man with mitral insufficiency due to ischemic cardiomyopathy. Acute myocardial failure precluded the successful discontinuation of by-pass despite the use of vasopressors.

Postoperatively all patients but one showed an immediate striking improvement in cardiovascular status. The one exception (Case 11) was a 49-year-old woman with long-standing mitral stenosis, severe pulmonary hypertension and right ventricular failure, who was taken to the operating room in a moribund state. Postoperatively evidence of severe and irreversible myocardial failure persisted, despite satisfactory oxygenation, correction of acid-base and electrolyte imbalance and administration of digitalis and isoproterenol. Progression of congestive failure resulted in death on the thirteenth postoperative day.

Two other postoperative deaths occurred. One patient died six days after aortic valve replace-

ment for gross aortic incompetence associated with incompletely treated endocarditis. Death was due to severe bronchopneumonia caused by pseudomonas. The other patient died on the fifth postoperative day of progressive hepatorenal failure following aortic valve replacement for terminal aortic stenosis.

The surviving patients are all asymptomatic after intervals of one to eighteen months (Table 1). One patient (Case 6) required reoperation one year postoperatively because of severe uncompensated hemolytic anemia secondary to an aortic periprosthetic leak. He has recovered.

Discussion

The patients described above illustrate the occasionally unpredictable and sudden hemodynamic deterioration which may occur in valvular heart disease. The majority had aortic valve disease with its recognized proclivity to rapid and intractable decompensation. It should be emphasized, however, that any variety of valvular involvement, including the disrupted prosthetic replacement, may terminate unexpectedly. This state constitutes a surgical emergency and requires prompt clinical recognition and aggressive management.

With deterioration under maximum medical therapy, surgical operation must not be delayed to the point of irreversible cardiopulmonary decompensation and secondary organ failure. These considerations are particularly important in the management of sudden and refractory heart failure associated with acute valvular insufficiency secondary to perforation of the aortic valve in endocarditis or disruption of a previously implanted prosthetic valve. Medical treatment in this situation is usually totally ineffective and may further jeopardize the patient in a low cardiac output state.

Despite the advanced state of heart failure present in these patients, gratifying results may follow emergency operation. All but two had immediate and dramatic improvement following valve replacement, and all surviving patients are fully active at present. The patients who did not survive presented either severe myocardial disease (Case 11) or extreme secondary organ involvement which did not reverse in the immediate postoperative period. It should be noted, however, that preoperative evaluation could not predict the ultimate clinical outcome. Thus, only separate and clearly irreversible complicating factors should preclude attempts at surgical management.

Psychotherapeutic Drugs

Use Among Adults in California

DEAN I. MANHEIMER, M.A., AND GLEN D. MELLINGER, PH.D., *Berkeley*;
AND MITCHELL B. BALTER, PH.D., *Chevy Chase, Maryland*

■ *A cross-section survey of adults in California provides the following information about use of prescription and non-prescription stimulants, sedatives, and tranquilizers.*

- *One person in two has used one or more of these drugs at one time or another. About three persons in ten have used them in the past 12 months.*

- *Frequent use is reported by 17 percent of the adults sampled and occurs among almost twice as many women as men.*

- *Relatively high proportions of frequent drug users are also found among persons who are divorced or separated, and among those with no religious affiliation. Relatively low proportions are found among persons in skilled, semi-skilled and unskilled occupations.*

- *Contrary to expectation, neither income nor education is very highly related to frequent use of psychoactive drugs. Actual differences may be obscured, however, by the fact that questions in this preliminary investigation combined both prescription and non-prescription drugs. Early returns from a survey now going on in San Francisco indicate that use of ethical drugs is indeed more common in better educated and higher income groups.*

- *Patterns of frequent drug use by age clearly reflect changing needs and stresses. Men, for example, are most likely to report use of stimulants in their 30s, tranquilizers in their 40s and 50s, and sedatives from age 60 on.*

- *Data suggest that persons in low status socio-economic groups are less likely than others to have used psychoactive drugs (in particular, tranquilizers), but those who use them are more likely to have done so frequently. One explanation offered was that these persons do not have as ready access to such drugs as others do. Consequently, there is a selective factor operating: only those whose need for drugs is relatively great actually get them.*

DATA ON USE of psychotherapeutic drugs in California were obtained in a preliminary investigation conducted in preparation for a more intensive series of studies in this state and elsewhere.

It is well known that there has been a dramatic increase in recent years in the use of psychotherapeutic drugs, especially the tranquilizers. Some indication of the extent to which these drugs are now used is given by the estimate that for the nation as a whole 167 million prescriptions for stimulants, sedatives, and tranquilizers were filled in 1965.* And a 1962 survey by the Food and Drug Administration reported that enough barbiturates alone were produced in that year to supply approximately 24 doses to every man, woman and child in the country.¹

Data such as these are often cited as evidence that we are becoming a "drug-dependent" society. They also have been used in supporting legislation to curb the "epidemic of drug abuse." Nevertheless, despite the widely publicized controversy over psychotherapeutic drugs, there is very little factual information about the use of these drugs—who is using them, how they are acquired, what they are being used for, and how they serve as one of many alternative (and possibly competing) ways of coping with the stresses of modern living.

In order to obtain this information, a series of studies is being undertaken to describe existing patterns of acquiring and using them. A major premise underlying these studies is that the problem of *drug abuse* cannot be adequately understood in the absence of normative data on *drug use*. For example, whether we can rightly be called a drug-dependent society depends on whether heavy use is concentrated among a few groups or is widespread.

The first study in the series is now being conducted in San Francisco. However, in planning the studies, preliminary data were needed to test certain basic assumptions about the distribution of the use of psychoactive agents in various segments of society. It was felt that such data would help us design our samples and would also provide useful research leads that we might otherwise overlook.

Submitted 22 January 1968.

From the Langley Porter Neuropsychiatric Institute, San Francisco. (Dr. Balter is with the Special Studies Section, Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase.)

The investigation was supported in whole by Public Health Service Research Grant No. MH-12591, National Institute of Mental Health.

Reprint requests to: Director, Family Research Center, 2180 Milvia Street, Berkeley 94704 (Manheimer).

*Estimate based on data obtained from the National Prescription Audit.

With this in mind, the two research organizations engaged in this collaborative effort* contracted with the Opinion Research Corporation in Princeton and the Field Research Corporation in San Francisco to add a few "rider" questions to their regular surveys. The Opinion Research Corporation survey was done in May 1967 with a cross-section nationwide sample; the Field Study was done in June 1967, a few weeks later, with a cross-section statewide sample of households in California.

Study Methods

This paper reports on the findings of the California Study which was based on a sample comprising 1,026 persons 21 years or over and representing all non-institutionalized segments of the adult population. Some findings of the national study are referred to for comparison but the detailed results of the nationwide survey will be reported elsewhere.³

Several important methodological qualifications should be noted as background for interpreting the data reported in this article. In particular, we want to call attention to the possibility that the relatively simple polling techniques used to obtain these data may tend to underestimate actual levels of drug use.

The research teams engaged in this project have spent a great deal of time developing and pre-testing questions on drug use in preparation for a series of more intensive community studies. These pre-tests demonstrate that great care must be taken to obtain accurate reporting of drug use in household surveys, especially since the extent of bias may differ among various types of respondents. Older respondents, for example, may be reluctant to admit drug use because of its association (real or imagined) with "dope addiction." There are other subgroups in which the use of psychotherapeutic drugs is more socially acceptable and in which there would be less tendency to under-report the use of drugs. Even more important, perhaps, are differences in under-reporting due to varying degrees of knowledge about and awareness of the psychotherapeutic drugs.

In pre-tests for the community studies we found that two devices are essential in order to obtain reliable data on the use of psychotherapeutic drugs. First, questions on drug use are preceded by a

*The Family Research Center of the Langley Porter Neuropsychiatric Institute (San Francisco) and the Social Research Group of the George Washington University (Washington, D. C.).

series of "warm-up" questions that gradually and logically lead into drug use, thereby allowing the interviewer to establish good rapport with the respondent before broaching the subject. And second, we use a chart showing the most commonly used psychotherapeutic drugs in their actual size and color. The evidence we have so far indicates that the chart is exceedingly effective in helping respondents to recall the drugs they have taken and to identify them by name.

The reader should also be reminded that the questions on drugs used in this study did not distinguish between prescription and non-prescription (over-the-counter) drugs. This would tend to obscure certain differences if, as we suspect, poorer and less well educated persons are more likely to use over-the-counter remedies than those who are more affluent and better educated. The studies now going on will, of course, differentiate these two types of drugs.

Given these qualifications, the data reported here probably provide minimum estimates of drug use. Even though there may be differential under-reporting in various population subgroups, the findings can provide a useful basis for hypotheses

to be explored more vigorously in later studies.*

Findings

Drug users were classified into three overlapping groups: (a) those who have ever used one or more of the three types of drugs—stimulants, sedatives, or tranquilizers, (b) those who have used at least one of the drugs frequently, and (c) those who have used one or more of the drugs in the past 12 months. (See Table 1.)

Ever Used: At one time or another every other adult in California has taken a stimulant, sedative or tranquilizer.

Used Frequently: Almost two in ten (17 percent) report having taken one of these drugs frequently, i.e., "regularly" or "fairly often."

Used in Past 12 Months: About three persons in ten have used one or more of these drugs in the past year.

The data to the right in Table 1 shows use in the past 12 months based on national data ob-

*No tests of statistical significance were applied to the data because the sampling procedure did not use probability methods in the final stage of sampling, and such tests are therefore not appropriate. Further, the purpose of the study was to develop rather than test hypotheses.

TABLE 1.—Use of Three Drug Types Among California Adults: Proportion Having Used Each Drug Type (a) Ever, (b) Frequently, and (c) in the Past 12 Months

	Used Each Drug Type:			
	(a)	(b)	(c)	National (ORC†)
	Ever	Frequently	In Past 12 Months	Data: Past 12 Months
	%	%	%	%
Used at Least One of the Three Types of Drugs*	51	17	29	24
Stimulants‡	(19)	(6)	(9)	(6)
Sedatives	(29)	(7)	(16)	(11)
Tranquilizers	(29)	(10)	(19)	(15)
Used None	49	83	71	76
Total %	100	100	100	100
Total Interviews (Base for %s)	1,026	1,026	1,026	2,071

The California data were based on replies to the following questions:

Have you ever used any pills or medicines one or more times that help you stay awake, pep you up, help you lose weight, or cheer you up; pills that are often called *stimulants*, such as Dexamyl, Dexedrine, Elavil, Preludin, No-Doz, and the like?

Have you ever used any *sedatives* or *sleeping pills* one or more times, such as Seconal, Phenobarbital, Doriden, Sleep-Eze, and the like?§

Have you ever used any pills or medicines one or more times to help you calm down or keep you from

getting nervous and upset; pills that are often called *tranquilizers*, such as Miltown, Equanil, Librium, Compoz, and the like?

For each affirmative answer to the above questions the respondent was asked:

Would you say you have used one fairly regularly, not regularly but fairly often, not very often, or just once or twice in your whole life?

When was the last time you used a pill or medicine like that—was it 12 months ago or less, between a year to 3 years ago, or over 3 years ago?

*These figures are less than the sum of the three percentages shown for the specific drug types since some persons used more than one type.

†Opinion Research Corp.

‡As can be seen in the question, this category includes anti-depressants and anorexants.

§This question was also asked in the following alternative form with a random half of the sample: "Have you ever used any pills or medicines one or more times to help you sleep at night; pills that are often called sedatives such as Seconal, Phenobarbital, Doriden, Sleep-Eze, and the like"? This latter wording proved to be somewhat less sensitive than the other version and produced slightly fewer affirmative responses. Nevertheless, the results obtained from these two versions have been combined in order to avoid complicating the presentation unduly.

tained by Opinion Research Corp. (ORC) within a month of the California poll. A comparison of the California and national data shows California to be somewhat higher than the rest of the country in use of each of the three types of drugs.

Sedatives and tranquilizers have been used at one time or another by more people than have stimulants—about three persons in ten compared with two in ten. In view of the fact that tranquilizers are a relatively new arrival on the phar-

macological scene, it is interesting that they have been used by as many people as sedatives have been. The growing popularity of tranquilizers is also suggested by the fact that slightly more people have used drugs of this type during the past year than have used sedatives.

Although fewer people have ever used stimulants than the other drugs, it appears that frequent use occurs about as often with stimulants as it does with sedatives. Frequent use of stimulants

TABLE 2.—*Proportion of Adults in California and in Selected Subgroups Reporting Frequent Use of One or More of Three Drug Types—Stimulants, Sedatives, and Tranquilizers*

	<i>Stimulants %</i>	<i>Sedatives %</i>	<i>Tranquilizers %</i>	<i>Any of the Three %</i>	<i>(Base for Percents)</i>
ALL ADULTS	6	7	10	17	1,026
SEX					
Male	4	5	6	12	527
Female	8	8	14	22	499
AGE					
21-29	8	3	7	13	210
30-39	10	4	12	21	197
40-49	6	7	11	17	230
50-59	4	8	11	18	161
60+	2	11	8	16	228
MARITAL STATUS					
Married	6	6	10	16	813
Single	7	7	3	14	73
Widowed	4	14	10	20	80
Separated-Divorced	8	10	18	27	60
RACE					
White	6	7	9	17	909
Negro	5	10	15	19	78
Other	5	5	13	15	39
RELIGION					
Protestant					
Fundamentalist	6	6	8	16	210
Other	5	7	10	16	382
Roman Catholic	6	6	9	16	301
Jewish	2	9	14	18	44
Other or None	12	8	12	25	89
EDUCATION					
<High School Graduate	4	8	10	16	315
High School Graduate	5	6	9	16	287
Some College	9	6	9	19	255
College Graduate or More	7	6	11	17	169
FAMILY INCOME*					
< 3000	5	10	10	19	122
3 < 5,000	6	5	8	14	118
5 < 7,000	6	8	9	18	171
7 < 10,000	6	5	11	16	227
10 < 15,000	7	5	8	16	238
15,000 or more	5	8	11	20	134
RESPONDENT'S OCCUPATION					
Professional, Technician, etc.	8	6	8	17	192
Clerical	8	10	9	18	79
Sales	9	9	10	22	67
Skilled Craftsmen	5	4	2	9	97
Service and Semi-skilled	3	1	9	12	98
Laborers	0	0	3	3	37
Males Not in Labor Force	1	11	8	16	118
Females Not in Labor Force	7	7	14	21	338

*Omitted from this table were 16 persons for whom income data were not ascertained.

is reported by 6 percent of the adult California population, as compared with 7 percent for sedatives and 10 percent for tranquilizers.

One of the main interests in our research program is in the use of drugs as one means of coping with the recurring stresses of everyday living. For this reason we are more interested in *frequent* drug use than we are in occasional use and we will therefore focus the rest of the article on the frequent users as distinguished from the "occasional users"—those who report using a psychotherapeutic drug "not very often" or "just once or twice" in their whole lives.

Frequent Drug Use in Various Subgroups

Table 2 indicates levels of frequent use of stimulants, sedatives, and tranquilizers according to a number of background variables.

Sex. Men and women differ sharply in their use of psychotherapeutic drugs. Almost twice as many women as men are frequent users of one or more of the three classes of drugs investigated (22 percent against 12 percent). This disparity is found for each of the three classes of drugs and is greatest for tranquilizers. The greater use of drugs by women contrasts sharply with the available evidence regarding drinking. Cahalan, for example, finds that women are less likely than men to cope with their everyday problems by drinking.²

Age. Frequent use of stimulants is reported most often by younger people—particularly those in their thirties. Sedatives, on the other hand, are used frequently by very few persons under 40 but are popular among those 60 or over.* About one in ten among this latter group has used sedatives regularly or fairly often. Still another age pattern is found for tranquilizers: frequent use is greater among persons in their middle years, while adults under 30 and persons 60 or more are the least likely to use tranquilizers frequently.

Marital Status. The widely differing patterns of living associated with marital status are clearly reflected in levels of frequent drug use. Persons who are currently separated or divorced, for example, are more likely to report frequent use of one or more of the drugs than are married or single persons.* This difference is most evident in the use of tranquilizers: 18 percent of those who are divorced or separated say they have used tran-

quilizers frequently, as compared with 10 percent of married persons and only 3 percent of those who are single. These findings are consistent with studies showing that divorced members of our society have a disproportionate share of physical and mental health problems. Although they seldom use tranquilizers, single persons are close to the overall average in their use of stimulants and sedatives. Persons who are widowed tend to use sedatives somewhat more often than others—a reflection, perhaps, of their older age.

Race. When we look at frequent use by race for all three drugs combined, we find no appreciable differences between whites, Negroes and others, although the proportions using tranquilizers tend to be higher among Negroes than among whites.* Even though differences between whites and Negroes on frequent use are relatively minor, data shown later indicate that many more whites than Negroes have *ever* used one or more of the drugs. (This finding will be discussed later in more detail.)

Religion. In general, religious affiliation shows little relationship to frequent drug use, except that those who profess no affiliation are more likely than others to use stimulants. Although there are too few Jewish respondents in the sample to generalize, it appears that very few of them have used stimulants and relatively many have used tranquilizers frequently.

Income and Education. It is widely assumed that use of psychotherapeutic drugs is most common among well educated persons with relatively high incomes. This assumption is not, by and large, supported by the data. The only difference worth noting is that college-educated persons are somewhat more likely to use stimulants than are people with less education. No clear-cut relation between income and drug use was shown. Differences undoubtedly would be greater if the analysis were limited to the drugs obtainable only on prescription.

Occupation. Even though frequent drug use is not highly related to income and education, we do find meaningful differences by occupation. Overall, use is less common among persons in occupations of lower status. It is interesting that at the higher end of the occupation scale, persons in clerical and sales occupations report using drugs

*This interpretation of the data assumes that persons who use drugs frequently have, for the most part, used them in recent years. Data not shown support this assumption.

*On the basis of early returns from the San Francisco Study, it is worth noting that use of psychotherapeutic drugs by Negro men seems to be heavily concentrated on the non-prescription drugs—No-Doz, Sleep-Eze, and so on.

TABLE 3.—*Proportion of Adults Reporting Frequent Use of One or More of Three Drug Types—Stimulants, Sedatives, and Tranquilizers—Shown Separately for Men and Women by Age*

Age	Stimulants %		Sedatives %		Tranquilizers %		Any of the Three %		(Base for Percents)	
	M	F	M	F	M	F	M	F	M	F
21-29	4	12	3	3	2	13	8	20	118	92
30-39	8	12	0	6	5	18	13	27	87	110
40-49	5	7	7	8	10	12	15	19	105	125
50-59	2	5	6	10	7	15	12	24	82	79
60 +	0	4	10	13	7	10	13	19	135	93
TOTAL	4	8	5	8	6	14	12	22	527	499

at least as often as those in professional, managerial and technical positions.

Drug Use in Various Subgroups of Men and Women

We have observed that men and women differ sharply in their use of psychotherapeutic drugs. Another step in the analysis was therefore to determine whether this difference holds up in various population subgroups as defined by variables shown in Table 2 as well as other variables.

Age by Sex. Table 3 compares drug use by men and women in each of the five age categories. In most age groups, and for each of the three types of drugs investigated, women are more likely to be frequent users than are men. However, use patterns according to age are not always identical for both sexes. Thus it appears that men are most likely to report use of stimulants in their thirties, of tranquilizers in their forties and fifties, and of sedatives from age sixty on—a pattern that clearly reflects the changing demands and stresses that men experience in the course of their careers.

Women, on the other hand, are most likely to report use of stimulants throughout the age period 21 through 39—often, presumably, as a means of weight control. And frequent use of tranquilizers occurs most often among women in their thirties, with another peak in use (at a somewhat lower level) again during the fifties. With respect to sedatives, use patterns are similar for men and women — the proportion of frequent users increases steadily with advancing age.

Working Status by Sex. One of the few exceptions to the general rule that more women use psy-

chotherapeutic drugs than do men is shown in Table 4. Thus women who are not in the labor force tend to be somewhat less likely to use sedatives than their counterparts among the men. This slight departure from the general trend is probably an artifact due to age, since men who are not in the labor force are likely to be retired and therefore older, on the average, than the women—most of whom are housewives.

A more interesting finding in this table involves a comparison between women who are in the labor force and those who are not. Surveys of drinking behavior and smoking patterns have found that women who work tend to take on male patterns of alcohol consumption and smoking. As applied to drug use, this might lead one to expect that working women would be less likely to use drugs than women who do not work. This expectation is not borne out by the data, however. The differences are small but, for stimulants and sedatives, tend to be in the direction of greater drug use among working women. Thus the apparent reluctance of men to use psychotherapeutic drugs as a means of coping with stress does not seem to be taken over by women who enter the working world.

Relation Between Access to Drugs and Use

In the data presented so far we have been concerned mainly with frequent drug use without regard to the proportion having *ever* used drugs. However, another set of data suggests an interesting hypothesis about the use of psychotherapeutic drugs among persons in low socio-economic status (SES) groups.

We know that persons in these groups have less

TABLE 4.—*Proportion of Adults Reporting Frequent Use of Drugs Shown by Work Force Status and Sex*

	Stimulants %	Sedatives %	Tranquilizers %	Any of the Three %	(Base for Percents)
ALL MEN	4	5	6	12	527
In labor force	4	4	5	11	409
Not in labor force	1	11	8	16	118
ALL WOMEN	8	8	14	22	499
In labor force	11	9	12	24	161
Not in labor force	7	7	14	21	338

TABLE 5.—Frequent Use of Tranquilizers In Selected Subgroups

		Use of Tranquilizers			
		%	Ever (Base)	Frequently %	(Base*)
ALL ADULTS	30	1,026	32	307
Nonwhite	24	117	61	28
Less than High School Graduate	25	315	39	80
Semi-skilled, unskilled and service occupations	20	135	37	27
Men in households with less than \$5000 yearly income	...	15	111	41	17

*The base for percentages in each group in this column is the number of persons in the group who have ever used tranquilizers.

frequent contact than others with physicians,* and for this reason their access to drugs is presumably more limited. If this reasoning is correct, we would expect to find that (a) persons in low SES groups are less likely than others to use psychotherapeutic drugs; but (b) those persons in low SES groups who do use these drugs need them more by the time they get them and are therefore more likely to use them frequently than are persons in the population at large.

This hypothesis was suggested by the data in Table 5 shown for four low SES groups: nonwhites, persons who have not completed high school, persons in low status occupations, and men in households with less than \$5,000 yearly income. Members of each group are less likely to have *ever used* tranquilizers than the adult population at large. But those who *have* used tranquilizers are more likely to have done so frequently.† The only group in which the hypothesis is not supported is women

in households with less than \$5,000 yearly income. (Data not shown.)

We should also mention an alternative explanation of these findings which is based on the possibility, mentioned earlier, that under-reporting of drug use may be greater in some groups than in others. This explanation suggests that persons with little education are less likely than others to be familiar with psychoactive drugs and also less likely, for this reason, to report using them. However, there may be less under-reporting among such persons if they have used these drugs frequently. As a result, the ratio of "frequent use" to "ever used" would be correspondingly high. The later intensive studies should help to clarify this issue since the aids to respondent recall should reduce under-reporting.

REFERENCES

1. AMA Committee on Alcoholism and Addiction: Dependence on barbiturates and other sedative drugs, JAMA, 193:673, 23 Aug. 1965.
2. Cahalan, D., Cisin, I., and Crossley, H.: American Drinking Practices: A National Survey of Behavior and Attitudes Related to Alcoholic Beverages, Report No. 3, Social Research Group, the George Washington University, Washington, D. C., June 1967.
3. Parry, H. J.: Use of psychotropic drugs by U.S. adults. Public Health Reports, 83:10, 799-810, Oct. 1968.
4. The 1964 Immunization Survey. Report No. One: Immunization status and related characteristics of preschool children and their families. Prepared for the Los Angeles County Health Department by the Survey Research Center, University of California, Berkeley, California, June 1965.

*A statewide survey conducted in 1964 provides considerable evidence that persons in low socio-economic status groups are less likely than others to have a regular doctor and are less likely to obtain various kinds of medical care for themselves and their children.⁴

†Data shown are based on use of tranquilizers only and the pattern described is clearer for tranquilizers than for the other two types of drugs.

Immune Response

With Particular Reference to the Use of Multiple Antigens

PAUL F. WEHRLE, M.D., *Los Angeles*

■ *The increasing demand for preventive child health services and the general increase in international travel compel greater attention to the use of multiple antigens, both inactivated and live, when administered simultaneously. It appears that with the preparations currently licensed, multiple inactivated antigens may be given safely and with expectation of optimal effectiveness. DPT is a routine combination employed in combination with oral trivalent poliovaccine for primary immunization of infants and young children up to and including age six. Oral poliovirus vaccine and vaccinia may be administered at the time of the recall or booster dose of DPT vaccine during the second year of life, commonly at age 15 to 18 months.*

It is apparent from published data accumulated over many years that several antigens may be administered at the same time with adequate immunologic response. The minor differences in antibody response following simultaneous administration of live viral antigens is of unknown clinical importance. The primary reason for hesitancy in advocating greater use of multiple agents at this time is the theoretical consideration of possible neurotoxicity with those vaccines where the parent agent may have definite neurotoxicity. The question of possible additive or other harmful effects with measles, poliomyelitis, and rubella and mumps when given simultaneously can be answered only by carefully controlled studies involving close observation of the recipients with extension of these trials as data permit.

THE AVAILABILITY of several relatively new vaccines has directed attention toward developing im-

Dr. Wehrle is Hastings Professor of Pediatrics, University of Southern California School of Medicine, Los Angeles, and Chief Physician, Pediatric and Communicable Disease Services, Los Angeles County-University of Southern California Medical Center, Los Angeles.

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Reprint requests to: Department of Pediatrics, Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033.

proved schedules for immunization. The goal is to provide maximal host response with minimal reaction, and at the same time not unnecessarily complicate the immunization process for either the patient or the physician.

The need to provide protection routinely in this country against the eight diseases noted in Table 1 for which antigens are at present available has been amply demonstrated. The extension of com-

TABLE 1.—*Antigens Currently Available for Immunization*

FOR USE IN THE UNITED STATES	
INACTIVATED ANTIGENS	ATTENUATED VIRAL ANTIGENS
Diphtheria	Measles
Pertussis	Mumps
Tetanus	Poliomyelitis (OPV)
Poliomyelitis (IVP)	(Rubella)*
Influenza	
FOR OVERSEAS TRAVEL	
INACTIVATED ANTIGENS	ATTENUATED VIRAL ANTIGENS
Cholera	Yellow Fever
Typhoid	
Typhus	

*Licensure expected in 1969 or 1970.

prehensive health services employing these antigens to population groups poorly immunized in the past has presented problems, since appointments may be broken frequently, often for compelling reasons. For such persons the temptation is great to provide a maximum number of immunizations when the patient is in the office or clinic. The foreign traveler with additional requirements frequently appears in the office or clinic for the first time only a few days before departure, also complicating the usual planned sequence of immunizations. In addition to these problems, the newer techniques of purification of antigens will undoubtedly lead to the prospect of many highly specific antigens which theoretically could be included in a single injection of small volume.

To develop an understanding of some of the problems involved and the measures to insure adequate response, we must first review the characteristics of the immune response of the host and the factors which may influence this response which are inherent in the use of multiple antigens in the clinical situation.

Response to Inactivated Antigens

Following injection, antigen may be demonstrated within the cytoplasm of lymphocytes, macrophages, primitive reticulum cells and immature plasma cells. Of these, the plasma cell appears to be most important in the production of antibody. After a latent or induction phase lasting from one to several days the production of antibody begins, and the plasma cell appears most important in its production. During this productive phase, antibody levels increase and reach a point which is dependent upon the characteristics of the antigen administered, the route, the dose (whether in a single site or multiple simultaneous initial injections),

and whether an adjuvant such as alum or aluminum hydroxide has been included.¹

Although the site and mechanism of antibody production has been amply documented,^{2,3} there has been considerable doubt as to whether individual antigens have separate "populations" of lymphocytes and plasma cells serving for immunologic memory and antibody production respectively, or whether a single population of cells within the host may respond to several antigens simultaneously. Recent data suggest that a single cell is capable of producing at least two separate antigens simultaneously.⁴ In the test situation described by Michael and Marcus it was apparent that two antigens provided simultaneous stimulation of a large proportion of single individual cells to produce two separate and distinct antibodies, although the actual amount of each antibody produced was less than that when the cell was engaged in producing a single type in response to a single antigen.

Effect of Multiple Antigens Given Simultaneously

More than 50 years ago it was found that experimental animals could respond to more than a single antigen simultaneously. These early data suggested that the host response in the intact animal was sometimes less when multiple antigens were given in combination than when each antigen was given individually. Studies including up to 35 antigens administered simultaneously have indicated that the response to a single agent may be adequate in a combination, although a "crowding out" effect may be seen when an excessive concentration of a single antigen is included in the mixture. In this latter situation it would appear that the individual devotes an excessive amount of energy toward production of antibody in response to the antigen in excessive dosage to the detriment of response to others in the mixture. This phenomenon has been shown particularly clearly when the test animals had previously received a primary dose of one of the antigens included in the mixture. The secondary response to this antigen was associated with decreased response to the other antigens.^{5,6,7} Further studies of this "crowding out" or interfering phenomenon among inactivated antigens have suggested that adjusting the amount of antigen administered and beginning immunization simultaneously with several antigens in proportional amounts avoids clinically important interference. Indeed, the adjuvant effect of pertussis antigen when included with diphtheria and pertussis has

been noted to enhance the response to diphtheria antigen with this combination.⁸ However, it should be noted that with large quantities of pertussis antigen, even in this mixture, it is possible to depress the response to tetanus and diphtheria toxoid.⁹

It would appear that, using the currently available inactivated antigens, it is possible to give pertussis, diphtheria, tetanus and the three polioviruses simultaneously without untoward effect and with at least the customary response.^{10,11} However, these mixtures may lack stability after prolonged storage and are not at present recommended for use. With the mixture of diphtheria, tetanus and pertussis currently available, it would appear that the toxoid response may be enhanced somewhat by the incorporation of pertussis vaccine.^{12,13} Insufficient data are available concerning simultaneous administration of adult type diphtheria, tetanus, cholera, typhoid, and typhus vaccines to permit firm conclusions. The immunologic response following simultaneous administration of tetanus, diphtheria, typhoid, paratyphoid A and B and three inactivated poliovirus antigens was adequate for all except for a relatively poor response to the typhoid and paratyphoid A and B components,¹⁴ this deficiency perhaps reflecting earlier immunization with other vaccine components.

Although only of historic interest currently, it should be noted that the three poliovirus antigens and inactivated measles vaccines, when administered simultaneously, produced serologic responses comparable to the responses evoked by these antigens when used individually.^{15,16}

Spacing of Multiple Antigens

As noted above, if the individual has had previous experience with one of the antigens represented in a combination of inactivated antigens depression in expected response may occur with those antigens administered for the first time. Until more information is available, it would be desirable to administer at least some inactivated antigens simultaneously. An example of an inappropriate schedule might be the use of an initial dose of pertussis antigen given alone in an infant and then following it with diphtheria, tetanus and pertussis in combination. The preferable course would be to use DPT simultaneously. For the physician dealing with adults, it may be preferable to administer cholera and typhus vaccine to the international traveler in advance of adult type diphtheria-tetanus

toxoid, since the latter is more likely to result in a response of recall type due to previous experience with the antigens. However, it should be pointed out that these considerations may be largely theoretical and should not prevent the simultaneous use of these antigens should the traveler be departing for his destination within a short time and require at least some protection before departure.

Immunologic responsiveness is greater if the doses of vaccine administered during the primary immunization series are given at intervals separated by more than a few days or weeks. Dr. Jeannette Wilkins, in recent studies with pertussis vaccine, showed that two doses of the currently standardized vaccine given at 60-day or greater intervals to infants 2 months of age or older provide the same agglutinin responses as three doses given at 30-day intervals. If this holds true with other antigens, and if the response seen is as durable as that following larger numbers of doses, this may result in further simplification of schedules. Both in experimental animals and in man extension of the interval between doses in the primary series is likely to result in at least as great a response if the doses are separated by several weeks or months than if the doses are given at one-month intervals. By wider spacing of doses a secondary or booster effect is often seen, and the practical advantage of a response of this type is obvious. The often observed but wasteful practice of beginning schedules over again when patients fail their appointments should be avoided.

Age of Initial Immunization

The blanketing effect of passively acquired maternal antibody in newborn or young infants has been amply demonstrated against a number of inactivated antigens, given singly or in combination.¹⁷ This blanketing effect, although clearly depressing the initial response to several antigens, has no apparent effect upon reinforcing or booster doses given during subsequent months or years. Therefore, with inactivated antigens this factor appears to be clinically unimportant.

It should also be noted that the immune response of the newborn infant appears to be largely an IgM response, and that this characteristic response persists during the first few weeks of life. Furthermore, the ultimate antibody titers achieved are less than those of older infants or adults. This immunologic immaturity appears to be associated with a scarcity of plasma cells in tissues respon-

sible for antibody formation, and this deficiency may be the factor responsible for the relatively ineffective response. Indeed, it is important to note that the only clinical demonstration to date of possible immunologic paralysis in man was that of Provenzano, Wetterow, and Sullivan¹⁸ who suggested that immunologic tolerance against pertussis vaccine may have occurred in some infants receiving large numbers of doses (three to six) beginning within 24 hours of birth and continued at three-week intervals. Although immunologic paralysis in experimental animals was described in 1949 by Felton, it has not been believed important in man since excessive doses of antigen were required to induce this phenomenon in animals and the intravenous route appeared to be essential for most animals. Although it was originally thought that antibodies were being formed during immunologic paralysis, but were not demonstrable since they were bound so promptly by excess circulating antigen, it now appears that these concepts may be incorrect. There now is clear evidence for lack of any antibody production during immunologic paralysis¹⁹ and it appears that this is at least a theoretical possibility in man with large doses of antigen administered at an early age.

Untoward Effects Following Inactivated Vaccines

Reactions of consequence following the use of currently available inactivated antigens are almost unknown. It is important to note, however, that recently the administration of inactivated measles vaccine has been followed by untoward local and systemic reactions with subsequent attenuated measles vaccine immunization²⁰ or with naturally acquired infection. These reactions suggest that inactivated measles vaccine should no longer be used. Use of an experimental inactivated respiratory syncytial vaccine has been followed by increased frequency of symptomatic disease in infants subsequently encountering the natural infection.²¹ These observations suggest new facets of considerable importance in the prophylaxis of disease, and may lead to a better understanding of the role of IgA secretory antibody in prevention of disease as well as of IgG in the pathogenesis of some diseases.

In summary, it would appear that the use of several inactivated antigens is on a sound foundation, providing excessive concentrations of quantities of a single component in the mixture are not employed. It would further seem desirable to

avoid administering a mixture involving antigens to which the host has not had previous exposure in combination with one or more in which a primary sensitizing dose had been given months or years previously. Even in this latter situation, some response may be expected to each of the individual components in the mixture, although this response may not necessarily be comparable to that seen when that component is given individually.

Attenuated Viral Vaccines

Considerations with regard to the simultaneous administration of live attenuated viral antigens are quite different from those outlined above for the inactivated antigens. With the administration of live attenuated antigens, factors such as the presence of circulating passively acquired antibody against that agent, interference between viruses if more than a single live virus is administered at one time, and the theoretical consideration of the possible selection of more virulent particles during the replication of the vaccine strain in the host must be considered. Of these, the easiest to deal with on the basis of current data is the effect of circulating antibody upon efficacy of single or multiple live virus antigens.

The prompt neutralization of live or active viral vaccines may have a profound effect upon immunologic response to these agents during much of the first year of life. This inhibition of response has been clearly demonstrated by many investigators using live measles and mumps vaccine, and preliminary data are available concerning inhibition of rubella vaccine at ages less than one year as well. With respect to vaccinia, adequate host response has been seen in infants less than one year of age, although data clearly suggest that complication rates are somewhat higher during the first year of life than in infants immunized after they are a year old.²²

Consequently, it would appear undesirable to use presently available attenuated viral vaccines (measles and smallpox) at less than one year of age, with the obvious exception of the oral poliovirus strains. The latter appear to be safe and effective when administered to infants during the first few months of life. Immunologic response has been satisfactory and the period of infancy is a time when protection against poliomyelitis is most important.

Interference between live viruses was first dem-

onstrated in 1935 by Magrassi and by Hoskins. The discovery of interferon by Isaacs and Lindenman in 1957 indicated at least one possible mechanism for the observed viral interference. It is important to note that the vaccine strains of several of the currently licensed vaccines are particularly efficient, when compared with the wild viruses of the same type, in producing interferon in both man^{23,24} and tissue culture systems.²⁵ Despite this phenomenon, numerous investigations of poliomyelitis Types I, II and III when given simultaneously; combinations of poliovirus and attenuated measles virus;²⁶ poliomyelitis and smallpox;²⁷ vaccinia and yellow fever;^{28,29} measles and vaccinia;³⁰⁻³³ measles, smallpox, and yellow fever;³⁴ and measles and mumps³⁵ have indicated that combinations of various live viruses have been used with a relatively high degree of effectiveness as measured by circulating antibody response. With the several combinations noted, the only discernible effect has been a slight depression in the level of circulating antibody against one individual component of the mixture, most frequently with yellow fever or a depression in subsequent antibody titer but not in frequency of "takes," with vaccinia. The clinical importance of such relatively minor depressions of host response is not clear at this time.

It is of interest that simultaneous use of vaccinia and BCG vaccine has been followed by some increase in pustular reaction to BCG.³⁶

Some vaccine strains, notably polioviruses Types I, II and III, do not replicate as efficiently in the laboratory at elevated temperatures comparable to febrile episodes in man as do the wild or naturally occurring strains. It has been postulated by some investigators that administration of other antigens which may induce a febrile reaction may selectively favor a more virulent vaccine population by favoring an occasional virus particle of greater virulence. Whether this is of any importance, or whether, even if possible, the interferon response to vaccine strains may negate such an effect remains to be seen. Certainly the experimental data with oral poliovaccines and other attenuated viruses cited above, and the widespread use of oral poliovaccines with DPT vaccine,³⁷⁻³⁹ together with frequent unexplained febrile episodes among young infants, provide reassurance that this possibility is of little or no importance. Concern over possible additive effects of simultaneous administration of vaccines whose wild parent strains occasionally produce

encephalitis can be answered only by further experience. Examples of these might be mumps, measles and rubella. The data available at present are not sufficient to answer this question.

Further exploration of the simultaneous use of multiple live viral vaccines is urgently needed. At present, on the basis of both experimental data and widespread usage, poliomyelitis vaccine together with DPT or vaccinia or both may be administered simultaneously without fear of untoward reaction or complications. Data at present suggest that many other combinations of attenuated viruses may be employed in the future and their use must be explored in carefully observed populations with adequate laboratory controls.

Current recommendations for the use of multiple live viral antigens have been developed by the Public Health Service Committee on Immunization Practices. These recommendations are as follows:

Simultaneous Administration of Live Virus Vaccines:

Data on simultaneous administration of live virus vaccines are not sufficient to develop comprehensive recommendations; but there are obvious practical advantages to combining vaccines, and investigations are under way which should help to define optimal practices. When combined administration is indicated, available data do not suggest that undesirable responses will result. The following comment presents current attitudes toward scheduling vaccination with three major live virus vaccines — poliomyelitis, measles and smallpox.

It has been generally recommended that immunizations with live virus vaccines be separated by at least one month whenever possible. The rationale for this recommendation is the theory that superimposed reactions and diminished antibody responses might result if two or more live virus vaccines were given simultaneously. Ideally, the initial doses of oral poliovirus vaccine should have been given before a child reaches one year, the age for giving live attenuated measles virus vaccine. Administration of poliomyelitis and measles antigens should be separated by at least one month. It is likewise desirable to separate measles and smallpox vaccinations by one or more months because both of these antigens may produce febrile reactions.

When, however, immunization program effectiveness is hindered or when the threat of concurrent exposures exists, the relevant live virus vaccines should be given at the same time. Observations do not indicate that this will cause a significant increase in adverse reactions or depressed antibody responses to either antigen.

REFERENCES

1. Wilson, G. S., and Miles, A. A.: Principles of Bacteriology and Immunity, Williams and Wilkins, Baltimore, 1964, Vol. II, 1345-1394, 1964.
2. Gowans, J. L., and McGregor, D. D.: Immunological activities of lymphocytes, *Progr. Allergy*, 9:1-78, 1965.
3. Gowans, J. L., and Uhr, J. W.: Carriage of immunological memory by small lymphocytes in the rat, *J. Exp. Med.*, 124:1017-1030, 1966.
4. Michael, J. G., and Marcus, R.: Apparent production of two types of antibodies by a single cell, *Science*, 159:1247-1249, 1968.
5. Barr, M., and Llewellyn-Jones, M.: Factors influencing the development of potential immunity and the character of the secondary response, *Brit. J. Exp. Path.*, 32:231-245, 1951.
6. Barr, M., and Llewellyn-Jones, M.: Some factors influencing the response of animals to immunization with combined prophylactics, *Brit. J. Exp. Path.*, 34:12-22, 1953.
7. Barr, M., and Llewellyn-Jones, M.: Interference with antitoxic responses in immunization with combined prophylactics, *Brit. J. Exp. Path.*, 34:233-240, 1953.
8. Barr, M., and Llewellyn-Jones, M.: Some factors influencing the response to immunization with single and combined prophylactics, *Brit. J. Exp. Path.*, 36:147-154, 1955.
9. Bigler, J. A., and Werner, M.: Active immunization against tetanus and diphtheria in infants and children, *JAMA*, 116:2355-2366, 1941.
10. Barnes, J. M., and Holt, L. B.: Quantitative studies in diphtheria prophylaxis. Antigenic interaction: I. Simultaneous inoculations, *Brit. J. Exp. Path.*, 36:415-424, 1955.
11. Wilson, R. J., Moss, G. W. O., Potter, F. C., and MacLeod, D. R. E.: Diphtheria and tetanus toxoids combined with pertussis and poliomyelitis vaccines. Clinical trial of a quadruple antigen, *Canad. Med. Assn. J.*, 81:450-453, 1959.
12. Barrett, C. D., Jr., McLean, I. W., Jr., Malner, J. G., Timm, E. A., and Weiss, C. F.: Multiple antigen immunization of infants against poliomyelitis, diphtheria, pertussis, and tetanus. An evaluation of antibody responses of infants one day old to seven months of age at start of inoculations, *Pediatrics*, 30:720-736, 1962.
13. Volk, V. K.: Observations on the safety of multiple antigen preparations, *Amer. J. Hyg.*, 47:53, 1948.
14. Volk, V. K., Top, F. H., and Bunney, W. E.: Reinoculation with multiple antigen preparations of free-living children previously inoculated with multiple antigen preparations, *Amer. J. Public Health*, 43:821-832, 1953.
15. Bernard, J. G., Colobert, L., Darbon, A., Dioux, R., Doukhan, G., Girier, L., Montagnon, B., and Servant, P.: Etude immunologique de la vaccination associée antidiphtherique, antitetanique, antityphoparatyphoidique et antipoliomyelitique, *Bull. WHO*, 26:699-725, 1962.
16. Brown, G. C., and Kendrick, P. L.: Serologic response of infants to combined inactivated measles-poliomyelitis vaccine, *Amer. J. Public Health*, 55:1813-1818, 1965.
17. Warren, J., Feldman, H. A., Iezzoni, D., Fulginiti, V. A., and Conway, T.: The responses of children to combined measles-poliomyelitis vaccine, *JAMA*, 186:533-536, 1963.
18. di Sant'Agnes, P. A.: Combined immunization against diphtheria, tetanus and pertussis in newborn infants. I. Production of antibodies in early infancy, *Pediatrics*, 3:20, 1949. II. Duration of antibody levels, *Pediatrics*, 3:181, 1949; and III. Relationship of age to antibody production, *Pediatrics*, 3:333, 1949.
19. Provenzano, R. W., Wetterlow, L. H., and Sullivan, C. L.: Immunization and antibody response in the newborn infant. I. Pertussis inoculation within twenty-four hours of birth, *New Eng. J. Med.*, 273:959-965, 1965.
20. Medawar, P. B.: Immunological tolerance, *Science*, 133:303-306, 1961.
21. Isacson, P.: Data presented at the Gustav Stern Symposium on Perspectives in Virology, New York, 1968.
22. Chanock, R.: Data presented at the Gustav Stern Symposium on Perspectives in Virology, New York, 1968.
23. Neff, J. M., Lane, J. M., Pert, J. H., Moore, R., Millar, J. D., and Henderson, D. A.: Complications of smallpox vaccination. I. National survey in the United States, 1963, *New Eng. J. Med.*, 276:125-132, 1967.
24. Petralli, J. K., Merrigan, T. C., and Wilbur, J. R.: Circulating interferon after measles vaccination, *New Eng. J. Med.*, 273:198-201, 1965.
25. Wheelock, E. F., and Sibley, W. A.: Circulating virus interferon and antibody after vaccination with 17D strain of yellow fever vaccine, *New Eng. J. Med.*, 273:194-198, 1965.
26. DeMaeyer, E., and Enders, J.: Interferon in cell cultures infected with measles virus, *Proc. Soc. Exp. Biol. Med.*, 107:573-578, 1961.
27. Froeschle, J. E., and Casey, H.: Simultaneous administration of oral polio vaccine and globulin-modified attenuated measles-virus vaccine, *J. Pediatr.*, 66:1031-1034, 1965.
28. Winter, P. A. D., Mason, J. H., Kuhr, E., Schaafsma, A. W., Robinson, M., Saayman, L. R., and Spence, R. G.: Combined immunization against poliomyelitis, diphtheria, whooping cough, tetanus and smallpox, *South Afr. Med. J.*, pp. 513-515, 11 May 1963.
29. Meers, P. D.: Combined smallpox-17D yellow fever vaccine for scratch vaccination, *Transactions of the Royal Soc. Trop. Med. Hyg.*, 53:196-201, 1959.
30. Peltier, M.: Yellow fever vaccination, simple or associated with vaccination against smallpox, of the populations of French West Africa by the method of the Pasteur Institute of Dakar, *Amer. J. Public Health*, 37:1026-1032, 1947.
31. Budd, M. A., Scharrens, R. G., McGehee, R. F., and Gardner, P.: An evaluation of measles and smallpox vaccines simultaneously administered, *Amer. J. Public Health*, 57:80-86, 1967.
32. Sherman, P. M., Hendrickse, R. G., Montefiore, D., Peradze, T., and Coper, G.: Simultaneous administration of live measles virus vaccine and smallpox vaccine, *Brit. Med. J.*, 2:672-676, 1967.
33. Weibel, R. E., Stokes, J., Jr., Buynak, E. B., Hilleman, M. R., and Grunmeier, P. W.: Clinical laboratory experiences with combined dried live measles-smallpox vaccine, *Pediatrics*, 37:913-920, 1966.
34. Kalabus, F., Sansarriq, H., Lambin, P., Proulx, J., and Hillman, M.: Standardization and mass application of combined live measles-smallpox vaccine in upper Volta, *Amer. J. Epidemiol.*, 86:93-111, 1967.
35. Meyer, H. M., Hostetler, D. D., Jr., Bernheim, B. C., Rogers, N. C., Lambin, P., Chassary, A., Labusquiere, R., and Smadel, J. E.: Response of Volta children to jet inoculation of combined live measles, smallpox and yellow fever vaccines, *Bull. WHO*, 30:783-794, 1964.
36. Feshchenko, L. G.: Reactogenic and immunogenic properties of measles and mumps vaccines administered separately and in association, *Tr. Inst. Epidem. Paster.*, 28:301-306, 1964.
37. Moodie, A. S., and Cheng, G. K. K.: Concurrent BCG and smallpox vaccination in newborn babies, *Tubercle, Lond.*, 43:115-160, 1962.
38. Rethy, L., Marcozi, J., and Joo, I.: Sabin vaccine and combined DPT immunization, (Letter to the editor), *Lancet*, pp. 497-498, 27 Aug. 1960.
39. Kelerin, G., Rethy, L., Marcozi, J., and Pacsa, S.: Sabin vaccine and combined DPT immunization, (Letter to the editor), *Lancet*, p. 456, 25 Feb. 1961.
40. Benson, P. F., Butler, N. R., Costello, J. M., Urquhart, J., Pollock, T. M., Barr, M., Goffe, A. P., and Knight, G. J.: Vaccination in infancy with oral poliomyelitis vaccine and diphtheria, tetanus, pertussis vaccine, *Brit. Med. J.*, pp. 641-643, 9 Mar. 1963.

Mycosis Fungoides

Topical Use of Nitrogen Mustard in Recurrent Cases

FAYE D. ARUNDELL, M.D., AND WILLIAM H. CHAN, M.D., *Stanford*

■ *The management of the patient with mycosis fungoides requires a variety of therapeutic modalities depending on the stage of the disease. Topically applied nitrogen mustard in the early stages of the disease has a beneficial palliative effect. The effects of nitrogen mustard paintings in the later course of the disease have not been previously reported. In the present study, topically applied nitrogen mustard solution was used to control recurrences of mycosis fungoides following electron beam therapy in 11 patients. Each patient received whole body applications of freshly prepared 10 mg per 50 ml solution of mechlorethamine hydrochloride (a nitrogen mustard) in water daily for seven days. In all patients pruritus disappeared within the first week and ulcers and plaques improved or disappeared in two to four weeks. The seven-day courses of mechlorethamine paintings were repeated as recurrences were noted. Mycosis fungoides was controlled by this therapy for periods ranging up to 15 months.*

Absence of systemic toxicity, a low incidence of cutaneous irritation and application of the treatments at home make topical nitrogen mustard a useful adjunct in the management of the late stages of mycosis fungoides.

THE SUPPRESSIVE EFFECT of topical applications of nitrogen mustard in the early eczematous and plaque stages of mycosis fungoides has been well documented since its introduction by Haserick, Richardson and Grant in 1959.¹⁻⁴ The later stages require extensive superficial roentgen therapy or high-energy electron beam therapy.⁵

Patients with mycosis fungoides who have recurrences after x-ray or electron beam therapy

pose a therapeutic problem for dermatologists. Anti-metabolites and alkylating agents are effective palliative agents but undesirable systemic toxicity accompanies their use.

The present study describes the effect of topically applied nitrogen mustard in patients with mycosis fungoides in relapse who had previously received electron beam therapy.

Method

The patient's skin is cleansed of all lotions and ointments by a soap and water bath. The physician (or a specially trained relative of the patient) wears rubber gloves while mixing and applying

From the Department of Dermatology, Stanford University School of Medicine.

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Reprint requests to: Department of Dermatology, Stanford University School of Medicine, Stanford 94305 (Dr. Arundell).

the solution. The necessary equipment consists of a 50 ml medicine cup, a 10 ml syringe and 22 gauge needle, gauze squares, a hemostat, room temperature tap water and a 10 mg vial of the nitrogen mustard mechlorethamine hydrochloride.

The contents of one 10 mg vial of mechlorethamine hydrochloride is dissolved in 50 ml of tap water. The freshly prepared solution is immediately painted on the patient's whole body surface, using gauze held in a hemostat as an applicator. The paintings are repeated until the entire 50 ml of solution has been used for the single treatment. The solution is allowed to air-dry on the skin.

The patient is instructed to take a soap and water shower or bath within three hours to remove degradation products of the nitrogen mustard from the skin. Lubricating creams or lotions are applied as required for relief of dryness or pruritus. All lubricating products are washed off before the next nitrogen mustard treatment.

A course of topical mechlorethamine hydrochloride therapy consisted of one whole body painting daily for seven days. No other specific systemic medication or radiation therapy was administered during this treatment. A rest period of at least one week between courses permitted evaluation of results. Further courses of topical nitrogen mustard were administered as indicated by the patient's response.

The first course of topical mechlorethamine solution was performed by the physician, who instructed the patient and a responsible relative in the method of mixing and applying the solution. All repeated courses were carried out by the patients' relatives at home.

Results

In the 18 months from August 1966 to February 1968, 11 patients who had recurrent mycosis fungoides following electron beam therapy were treated with courses of topical nitrogen mustard paintings (Table 1). Six of the patients were women and five were men, their ages ranging from 44 to 76 years. Two patients had received three courses of electron beam therapy, four had had two courses, and five had had one course each. The total dose per patient ranged from 600 to 3,900 rads.

All of the 11 patients with recurrences had plaques of mycosis fungoides. In addition to plaques, one woman had ulcerated plaques, one man had ulcerated plaques and tumors, and one woman had generalized erythroderma. The shortest interval between the termination of electron beam therapy and the first course of topical nitrogen mustard was six weeks and the longest was five years.

In the 11 patients, the recurrent lesions of mycosis fungoides responded to some degree to topical nitrogen mustard. Pruritus disappeared within one week and plaques and ulcers improved or disappeared in two to four weeks. There were no prolonged remissions in these patients, but they were able to control pruritus and suppress their cutaneous lesions for periods of three to fifteen months with repeated courses of topical nitrogen mustard. Three patients had excellent response, with complete disappearance of lesions. In four patients the response was good. In the remaining four patients, although pruritus was controlled, approximately half of the plaques persisted in spite

TABLE 1.—Clinical Data on Topical Nitrogen Mustard Treatment of 11 Patients with Mycosis Fungoides

Case No.	Electron Beam Therapy				Interval Between Electron Beam and Topical Nitrogen Mustard	Topical Nitrogen Mustard Therapy			
	Age Yr.	Sex	Courses No.	Total dose Rads		Stage of Mycosis Fungoides	Courses No.	Duration Therapy	Response*
1.	57	F	3	3000 rads	2 months	plaques	14	15 months	excellent
2.	55	F	2	2725 rads	1.5 months	plaques	20	12 months	good
3.	55	M	3	3500 rads	3 months	plaques	3	12 months	fair
4.	52	M	1	2150 rads	3 months	plaques	7	7 months	good
5.	44	M	1	1600 rads	2 years	plaques	5	7 months	good
6.	76	F	2	2400 rads	6 months	plaques ulcers	4	4 months	excellent
7.	64	F	2	3900 rads	17 months	plaques	5	4 months	good
8.	70	M	1	1200 rads	28 months	plaques tumors ulcers	2	4 months	fair
9.	61	M	2	1700 rads	26 months	plaques	3	3 months	excellent
10.	60	F	1	600 rads	37 months	plaques	2	2 months	fair
11.	54	F	1	1400 rads	5 years	erythroderma plaques	2	1 month	fair

*Response: Excellent—no lesion, good—greater than 75% resolution of all lesions, Fair—50-75% resolution of all lesions.

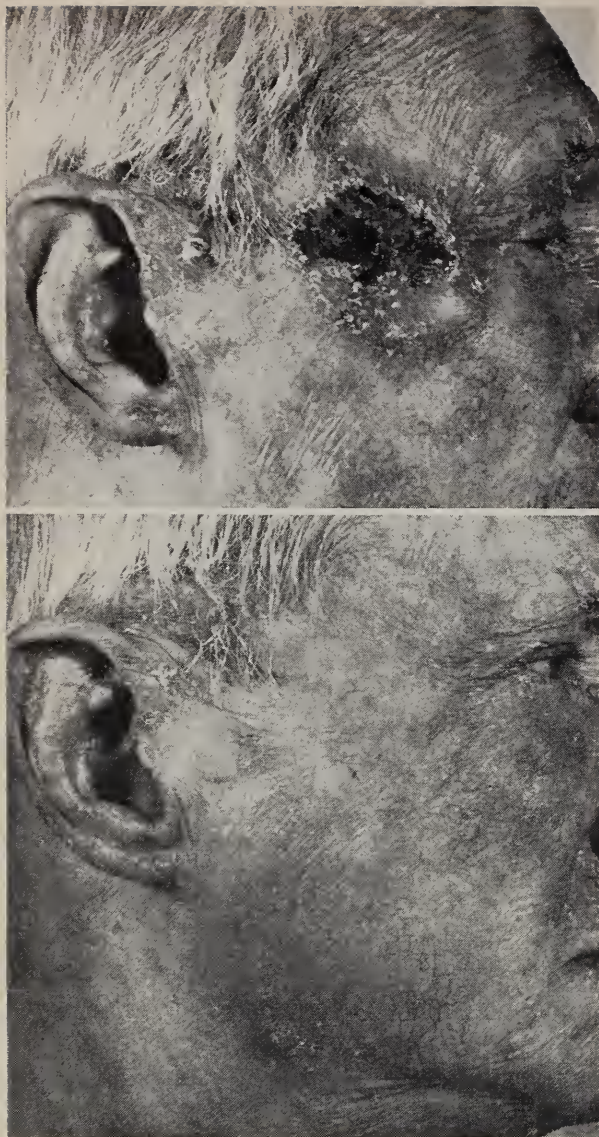


Figure 1.—*Upper*, ulcerated plaque of mycosis fungoides before topical nitrogen mustard therapy (Case 8, Table 1). *Below*, after two courses of topical nitrogen mustard.

of repeated courses of topical nitrogen mustard. Eroded and ulcerated plaques responded best to topical nitrogen mustard (Figure 1). Tumors and erythroderma did not respond.

In three patients (Cases 2, 5, 8) topical nitrogen mustard was discontinued after 12, 7, and 4 months, respectively, and another course of 1,000 to 1,950 rads of electron beam therapy was administered. Although mechlorethamine is classified as a radiomimetic drug, it did not interfere with the effectiveness of further electron beam therapy. Conversely, electron beam therapy in doses from 600 to 3,900 rads did not decrease the patients' tolerance to topical nitrogen mustard therapy.

There was a low incidence of undesirable side-effects in the 11 patients treated with mechlorethamine paintings. No systemic toxicity or depression of leukocytes in the blood occurred. In one patient (Case 3) acute dermatitis developed. Patch tests to old and fresh mechlorethamine solution were negative, and the patient was able to tolerate future nitrogen mustard paintings. Three patients complained of pruritus during the paintings; two of them were able to continue treatment, but the third, the woman with erythroderma, refused to continue. Summaries of three cases (Cases 2, 6, 7) are presented to illustrate the response to topical nitrogen mustard.

Case 2 (as shown in Table 1). A 55-year-old white woman first noted a red scaling eruption involving the thighs in January 1964. The diagnosis of mycosis fungoides, plaque stage, was confirmed by a skin biopsy in January 1965. In 1966 she received two courses of total body electron beam therapy from 10 January to 21 February (1,225 rads) and from 2 June to 21 June (1,500 rads) for a total dose of 2,725 rads. Five weeks after the second course of electron beam therapy there was a recurrence of plaques on the flanks, arms, thighs and legs. Topical nitrogen mustard was started on 10 August. Over the next 12 months, the patient received 20 courses of topical nitrogen mustard. Each course consisted of seven consecutive daily applications with a week's rest between courses. Response was good, and it was possible to delay a third course of electron beam for 12 months. On 7 September 1967 it was noted that she had thick infiltrated plaques on the trunk and hands. A third course of electron beam therapy (1,000 rads total body) was given between 25 September and 27 October, bringing the total dose to 3,725 rads. Two weeks after electron beam therapy, there was a recurrence of plaques on the trunk. Topical nitrogen mustard was resumed on 16 November 1967 in the same manner as before for six courses. Again response was good.

Case 6 (Table 1). A 76-year-old white woman had erythematous plaques on both soles in 1949. A skin biopsy on 13 January 1966 established the diagnosis of mycosis fungoides. Two courses of total body electron beam therapy were given, 20 January to 25 February 1966 (950 rads) and 16 March to 14 April 1967 (1,450 rads) for a total dose of 2,400 rads. Four months after electron beam therapy there was a recurrence of wide-

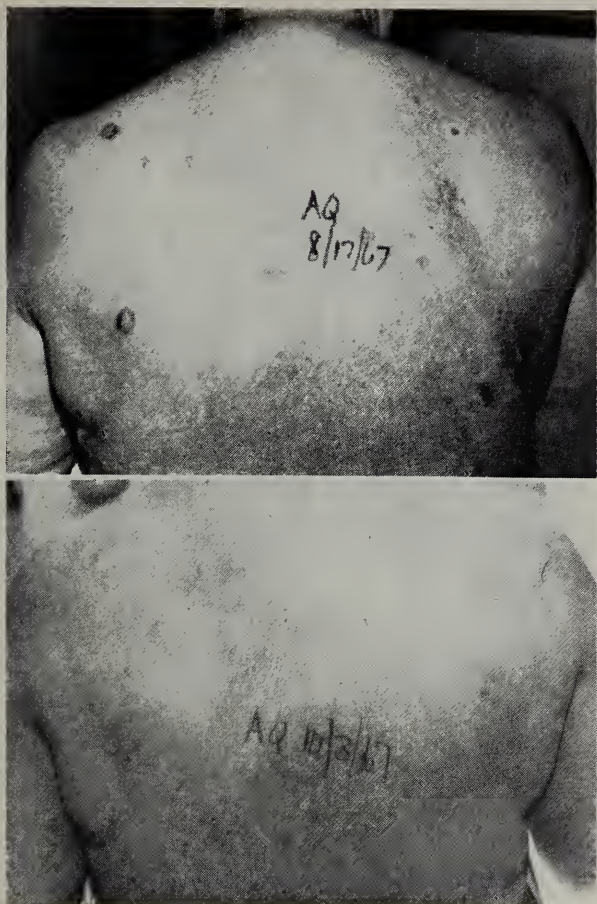


Figure 2.—Multiple plaques of mycosis fungoides before and after topically applied mechlorethamine solution (Case 7, Table 1).

spread plaques over the trunk, buttocks and thighs. Many plaques became eroded or ulcerated. On 4 October 1967 topical nitrogen mustard therapy was begun and the four courses were given. The patient bathed 15 minutes after each application because of pruritus and burning. Despite the early bathing there was an excellent response with complete clearing of lesions except for the lesions involving the left upper and lower eyelids, which were not treated with nitrogen mustard.

Case 7 (Table 1). A 64-year-old white woman began to have scaling plaques on the feet and legs in 1950. In 1963 a skin biopsy confirmed the diagnosis of mycosis fungoides. Two courses of total body electron beam therapy were given, one between 13 April and 28 May 1964 (2,400 rads), and the other 9 August to 10 September 1965 (1,500 rads) for a total dose of 3,900 rads. Plaques were noted on the legs, thighs, buttocks, back and upper extremities two months after the electron beam therapy. Topical corticosteroids of varying concentrations were used for the next 13

months. Nitrogen mustard paintings were started 21 February 1967. During the next four months the patient received five courses with a six weeks interval between the third and fourth courses. There was a 90 percent improvement (Figure 2). At the end of the four-month period, on 13 June 1967, therapy with intramuscular methotrexate was started. The patient did not respond. Topical nitrogen mustard therapy was resumed 31 August 1967, and the patient again had good response.

Discussion

Topical mechlorethamine solution had a suppressive effect in 11 patients with recurrences of mycosis fungoides. The patients had previously received up to 3,900 rads of electron beam therapy but this did not interfere with the effectiveness of topical nitrogen mustard therapy. In three patients mechlorethamine paintings did not affect tolerance to further courses of electron beam therapy, ranging up to an additional 1,950 rads in Case 8.

The pruritus in all patients was controlled by topical nitrogen mustard. As in previous reports³ plaques and eroded or ulcerated plaques gave the best responses. Erythroderma and tumors did not respond to this treatment.

The freshly prepared dilute solution of mechlorethamine hydrochloride used in this study did not result in the contact allergic sensitization which has been reported with more concentrated solutions.⁴ The immediate pruritus and discomfort which occurred in three patients during the applications were relieved by a soap and water bath as soon as the solution had dried on the skin. Early bathing, within 15 minutes, and the use of lubricating creams enabled two of the patients to continue therapy and did not diminish their response to nitrogen mustard paintings. The ease of preparation and application permitted home-use of topical nitrogen mustard therapy in our patients.

GENERIC AND TRADE NAMES OF DRUGS

Mechlorethamine hydrochloride—Mustargen®.
4-amino-N10-methylpteroylglutamic acid sodium —
Methotrexate sodium®.

REFERENCES

1. Haserick, J. R., Richardson, J. H., and Grant, D. J.: Remission of lesions in mycosis fungoides following topical applications of nitrogen mustard, *Cleveland Clin. Quart.*, 26:144-147, July 1959.
2. Madison, J. F., and Haserick, J. R.: Topically applied mechlorethamine on 12 dermatoses, *Arch. Derm.*, 86:663-667, Nov. 1962.
3. Sipos, K.: Painting treatment of nitrogen mustard in mycosis fungoides, *Dermatologica (Basel)*, 130:3-11, Jan. 1965.
4. Waldorf, D. S., Haynes, H., and Van Scott, E.: Cutaneous hypersensitivity and desensitization to mechlorethamine in patients with mycosis fungoides lymphoma, *Ann. Int. Med.*, 67:282-290, Aug. 1967.
5. Bagshaw, M. A., Schneidman, H. M., Farber, E. M., and Kaplan, H. S.: Electron beam therapy of mycosis fungoides, *Calif. Med.*, 95:292-297, Nov. 1961.

CASE REPORTS

Secondary Syphilis Misdiagnosed as Infectious Mononucleosis

MARCUS A. CONANT, M.D., AND
BARTON LANE, M.D., *San Francisco*

THE DIAGNOSIS of secondary syphilis is usually made on the basis of characteristic skin lesions, mucous patches or condylomata lata.^{1,3,6} Recent clinical experience suggests that the manifestations of early secondary syphilis are becoming fewer and milder.⁸ Numerous cases of secondary syphilis are now being seen with a few cutaneous manifestations or an atypical appearance. In the absence of characteristic skin lesions, early secondary syphilis may become manifest as a bizarre syndrome or it may mimic many systemic diseases. The following report is an example of a case of secondary syphilis which was misdiagnosed repeatedly over a period of four months as infectious mononucleosis.

Report of a Case

A 24-year-old single caucasian male postal employee was seen in the University of California Medical Clinic with a four-month history of headaches, malaise, anorexia, fatigue, sore throat and

gradually increasing left cervical adenopathy. He had also noticed an intermittent low grade fever to 38.3° C (101° F) and a non-pruritic evanescent erythematous eruption over the trunk which had been present for two days but had begun to clear at the time of our examination. For two weeks he had noted a white elevated plaque on the posterior tongue. He had been seen by three physicians during the four-month period, each of whom independently had diagnosed infectious mononucleosis. No blood tests were made nor drugs given until the patient was seen in the University Hospital Emergency Room one week before he was seen in our clinics. At that time, blood count was within normal limits, the sedimentation rate was 20 mm in one hour (Westergren) and a heterophile study was negative. He was given nystatin mouthwash to treat the plaque on his posterior tongue and sent home with a diagnosis of infectious mononucleosis and monilial stomatitis. The patient was referred to our clinic for additional evaluation.

The patient's past history revealed that 16 months previously he had been treated with penicillin for gonococcal urethritis. Twelve months previously he had been treated as a gonorrhea contact. Result of a VDRL test was negative on both occasions. His last sexual contact was two months before his visit to our clinic. He denied having genital lesions.

On physical examination he was seen to be a thin young man who did not appear chronically ill; there was visible left cervical adenopathy. Enlarged lymph nodes included the suboccipital, postauricular, preauricular, submandibular, posterior cervical, and supraclavicular groups, in addition to the inguinals and epitrochlears. The left cervical nodes were more prominent than the right. All nodes were movable, discrete, non-tender and of a "rubbery" consistency. On examination of the skin a faint erythematous morbilliform eruption

From the Division of Dermatology, Department of Medicine, University of California School of Medicine, and San Francisco General Hospital, San Francisco.

Submitted 17 June 1968.

Reprint requests to: Division of Dermatology, University of California San Francisco Medical Center, San Francisco 94122 (Dr. Conant).

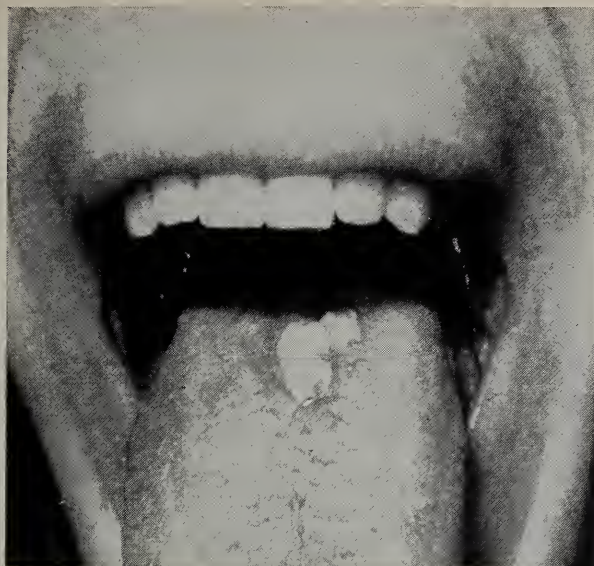


Figure 1.—Hypertrophic verrucous white lesion of tongue.

was noted on the trunk. Three 1-cm papulosquamous lesions were found on the frontal scalp, left forearm and chest. On the dorsal midline of the posterior half of the tongue was a hypertrophic verrucous white lesion (Figure 1). This was nontender and firm to palpation. Vessels of the pharynx and soft palate were engorged, and pharyngeal lymphoid tissue was somewhat hypertrophied. The tip of the spleen was felt two fingerbreadths below the left costal margin. There was no hepatomegaly. No lesions were found on the perineum or perianal area. The genitalia were also clear at the time of the first visit but three days later a 5-mm papule developed on the prepuce.

A blood cell count was within normal limits and the sedimentation rate was 12 mm in one hour (Westergren). No abnormalities were noted on urinalysis and a guaiac test of the stool was negative for occult blood. The serum icteric index was within normal range. Serum glutamic oxaloacetic transaminase (SGOT) was elevated at 48 Karmen units. The VDRL test was reactive at 1:64. Dark-field examination was positive for *Treponema pallidum* on the penile lesion, the tongue lesion and skin lesions on the left arm and chest.

The patient was treated with bicillin according to the schedule recommended by the U.S. Public Health Service. In addition, he was given 300,000 units of crystalline penicillin G in 2 percent aluminum monosterate (PAM) on the first visit to attempt to elicit a Herxheimer reaction. A typical Herxheimer reaction with chills and fever ensued (Table 1).

TABLE 1.—Record of Herxheimer reaction in Present Case

Time (hours after injection)	Temperature (° F)*	Symptoms (recorded by patient)
4	99.4	Chills
4½	100.2	Chills
5	101.0	Chills
5½	102.2	Chills with "flash"
6	102.2	Chills
6½	103.2	No chills
7	101.8	Cold sweats
7½	101.2	Chills and sweats
8	100.0	No chills
8½	99.4	Sweats
9½	98.6	Sweats
17½	98.6	Normal

*Temperature and symptoms were recorded by patient and are in his own words.

Improvement was rapid and all lesions had cleared completely in two weeks.

Discussion

The clinical manifestations of secondary syphilis reflect the initial reaction of the various body tissues to a spirochetemia; no doubt all of the tissues of the body are invaded in the early stages of syphilis.^{5,7} The skin manifestations are protean.¹ Mucous patches are common, but a hypertrophied, papillomatous condyloma on the posterior tongue, as described herein, is extremely rare.² Generalized lymphadenopathy occurs in 70 percent of cases and is one of the most characteristic aspects of the disease.⁶ Hepatitis and palpable hepatomegaly with or without jaundice occur occasionally in secondary syphilis; splenomegaly is more common.⁹ Liver involvement probably takes place much more frequently than is suspected clinically.

Significant constitutional symptoms occur in at least half the cases of secondary syphilis. Low grade fever may be intermittent or continuous. Headache, malaise, anorexia, weight loss and sore throat are all part of the clinical picture.^{1,6} The erythrocyte sedimentation rate is elevated in most cases. The differential diagnosis of such nonspecific constitutional symptoms includes many diseases, infectious mononucleosis, tuberculosis and brucellosis among them. In a few cases pyrexia of unknown origin may be the only complaint. according to Stokes and coworkers,⁶ the combined symptoms of sore throat and headache should suggest the possibility of secondary syphilis to the clinician. The sore throat and lymphadenopathy of syphilis must be kept in mind when mononucleosis is suspected.

In the case report presented, a patient with a

history of headache, fatigue, malaise, intermittent fever, anorexia, weight loss, sore throat and generalized adenopathy with splenomegaly was seen by several physicians and infectious mononucleosis was repeatedly diagnosed. A late-appearing syphilid on the tongue was diagnosed as thrush. The skin lesions were so slight as to be easily missed. Secondary syphilis had not been considered in the differential diagnosis; a VDRL test at the onset of illness would have saved the patient considerable time and expense and protected society from further spread of infection.

As suggested by Volan,⁸ the physician may sometimes have extreme difficulty in the differential diagnosis of early syphilis with atypical manifestations. This case is an example of how the physician might have made an early diagnosis by not forgetting syphilis and by broadening his indications for serological examination. Such indications should include VDRL tests in all cases of infectious mononucleosis-like syndromes, hepatitis, pityriasis rosea or fever of unknown origin.

REFERENCES

1. King, A., and Nicol, C.: *Venereal Disease*, F. A. Davis Co., Philadelphia, 1964.
2. Kingsbury, J.: *Dermochromes*, Vol. 111, Rebman Co., New York, 1921.
3. Olansky, S.: The diagnosis of early syphilis, *Med. Ann. DC*, 35: 367-368, July 1966.
4. Olansky, S.: Syphilis-rediscovered, *D M* 3-30, May 1967.
5. Sherlock, S.: *Diseases of the Liver and Biliary System*, ed. 2, Blackwell Scientific Pubs., Oxford, 1958.
6. Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: *Modern Clinical Syphilology*, ed. 3, W. B. Saunders Company, Philadelphia, 1944.
7. Thomas, E. W.: *Syphilis: Its Course and Management*, The Macmillan Company, New York, 1949.
8. Volan, H. H.: Diagnosis of early syphilis, *N. Y. State J. Med.*, 66:2908-2912, 15 Nov. 1966.
9. Weiss, R. S., and Joseph, H. L.: *Syphilis*, Thomas Nelson and Sons, New York, 1951.
10. Willcox, R. R.: *Textbook of Venereal Diseases and Treponematoses*, ed. 2, Charles C Thomas, Publisher, Springfield, 1964.

Congenital Pulmonary Lymphangiectasis

ROBERT S. ARKOFF, M.D., *San Francisco*

CONGENITAL PULMONARY LYMPHANGIECTASIS was first described by Virchow¹ in 1856. In a recent

review of this subject, Fronstin and associates² collected 32 cases from the literature in addition to the case they themselves reported. Four more cases have been reported since.³⁻⁶ Most of the reports of congenital pulmonary lymphangiectasis are to be found in the pathological literature. Until the present one, only 13 cases²⁻¹³ had been studied from a radiological standpoint and at least three of the 13 were complicated by other anomalies.

The present report concerns the diagnosis of an uncomplicated case of congenital pulmonary lymphangiectasis in the newborn period.

Embryology and Pathological Physiology

Between the twelfth and the sixteenth week of fetal life the pulmonary lymphatic tissue is well developed. Later the channels become narrower and the surrounding connective tissue diminishes. Lawrence¹⁴ expressed belief that congenital pulmonary lymphangiectasis stems from a continued growth of these tissues past the fetal stage. This theory appears to be better supported than that of Giammalvo,¹⁵ who postulated that this anomaly results from a failure or delay in linkage of isolated lymphatic spaces.

Theros⁶ correlated the pathological and radiological features of congenital pulmonary lymphangiectasis. Grossly, the lungs are bulky and inelastic. Large cystic spaces are apparent in the subpleural area. On sectioning, cystic lymphatic areas are also found peribronchially and in the interlobular septa. This results in a honeycomb appearance. Microscopically, an increase in fibrous tissue may be seen in addition to the dilated cystic lymphatic spaces. The surrounding alveoli are nearly collapsed and airless, although there may be bronchiolar ectasia.

Report of a Case

The patient was an 8-pound, full-term female infant who was delivered from a 39-year-old Caucasian who had had two previous uneventful pregnancies and healthy offspring. The current pregnancy was complicated by rupture of the membranes 24 hours before delivery. The fetal heart rate was noted to be irregular for four hours before the otherwise uncomplicated labor was terminated by application of outlet forceps. At birth the child did not cry or breathe vigorously and was deeply cyanotic. Respirations were 20 to 30 per minute. There was no chest retraction. Breath sounds, although diminished, were heard slightly better on the right. The heart rate was 80 to 100

From the Department of Radiology, Children's Hospital and Adult Medical Center, San Francisco.

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Reprint requests to: Department of Radiology, Children's Hospital and Adult Medical Center, 3700 California Street, San Francisco 94119.

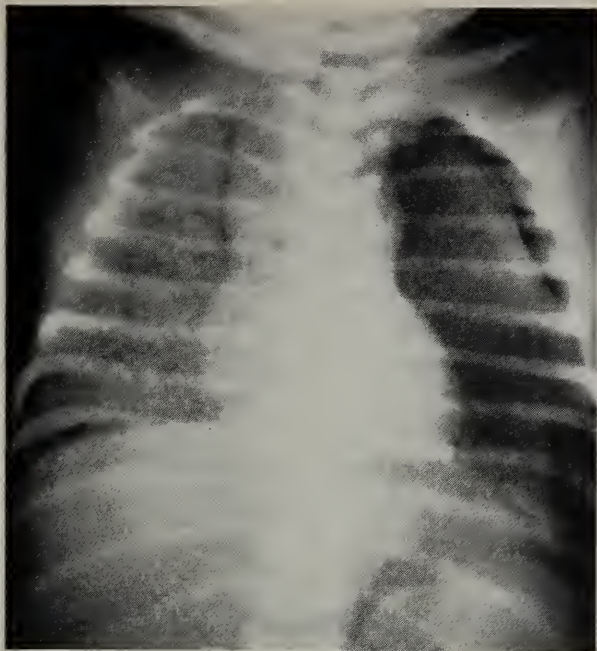


Figure 1.—Film at three hours of age shows generalized interstitial pattern. Interspersed radiolucent areas are probably focal areas of bronchiolar ectasia as well as acquired air cysts due to resuscitative effort. Note also left pneumothorax.

per minute. The liver was enlarged down to the umbilicus. Despite therapeutic measures, which included umbilical catheterization for fluid and bicarbonate administration, needle aspiration of left pneumothorax, oxygen therapy, and respiratory assistance with bag and mask and the Bennett respirator, the child died at 5½ hours of age.

Laboratory data included blood pH of 6.81 (normal 7.35 to 7.42). An electrocardiogram showed right ventricular activation time which was borderline to slightly prolonged and ST depression in leads V-1 to V-4 with inverted T.

An x-ray film of the chest (Figure 1) at three hours of age showed a generalized interstitial pattern of increased density, interpreted to be due to either lymphangiectasis or to anomalous pulmonary venous return with pulmonary edema. A moderate left pneumothorax and bullous changes on the right were believed to have been induced by resuscitative efforts. The clinical features and the radiographic findings appeared to fit best with congenital pulmonary lymphangiectasis.

At autopsy, the lungs appeared congested and edematous. The pleurae showed occasional small vesicles. On cross section the parenchyma was firm. The cut surface exuded a pink fluid. The interlobular septa were prominent.

On microscopic examination (Figure 2), di-

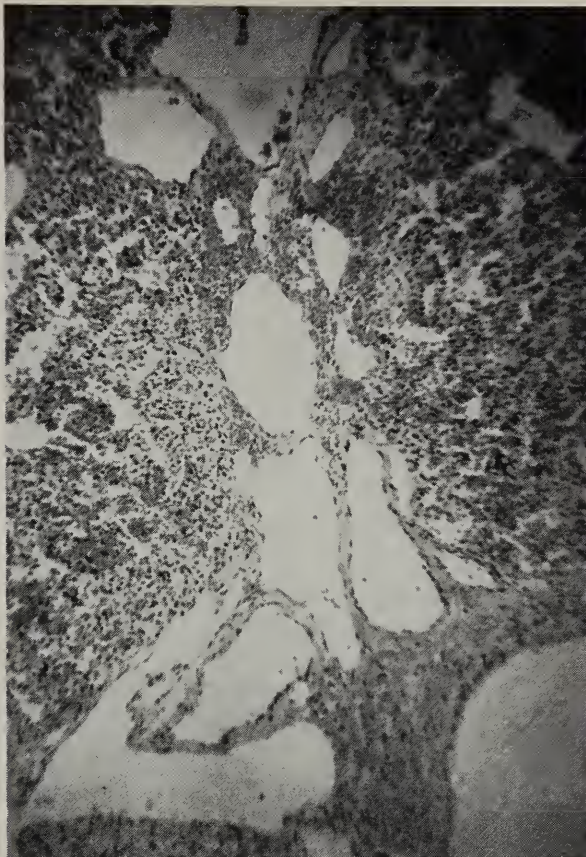


Figure 2.—Dilated clear spaces lined by a single layer of flattened endothelium are present subpleurally and along the interlobular septa.

lated clear spaces were present in the subpleural area with extensions along the interlobular septa. These spaces, which were up to 2.5 mm across, were lined with a single-layered, flattened endothelium. The alveoli were poorly expanded and contained many intact red blood cells. The bronchial epithelium was intact and the alveolar ducts were not prominent. The pathological diagnosis was congenital pulmonary lymphangiectasis.

Roentgen Diagnosis

Uncomplicated congenital pulmonary lymphangiectasis presents a radiological appearance of generalized interstitial densities. Interspersed may be lucent cystic areas representing dilated bronchioles and alveolar ducts. The diaphragms are either normal in position or depressed. The presence of pneumothorax is not surprising in view of the extreme inelasticity of the lungs, although only two previous instances of pneumothorax have been reported in cases of congenital pulmonary lymphangiectasis.^{3,6}

Increased alveolar density due to compressed

air spaces or superimposed hemorrhage or pneumonia should not interfere with the recognition of the basic interstitial changes in congenital pulmonary lymphangiectasis.

Differential Diagnosis

Several somewhat similar conditions must be considered in differential diagnosis:

Primary lack of expansion or *fetal atelectasis* is marked not only by poor aeration, but by high position of the diaphragms, features which distinguish it from congenital pulmonary lymphangiectasis.

Neonatal pneumonia, particularly when due to aspiration, results in great variations in aeration in which focal emphysema is a prominent feature. Congenital pneumonia may be alveolar or interstitial, but in early stages rarely causes the profound cyanosis seen in congenital pulmonary lymphangiectasis.

Congenital cardiac anomalies, when causing neonatal distress, as a rule present with a pattern of interstitial and alveolar congestion and usually cardiomegaly. An exception to this is the presence of anomalous pulmonary venous return with pulmonary hypertension, such as occurs with drainage to the portal system. The roentgen findings may then mimic those of pulmonary lymphangiectasis. When congenital heart disease coexists with congenital pulmonary lymphangiectasis, correct diagnosis will be most difficult.

The premortem diagnosis of *pulmonary hemorrhage* in the newborn is difficult because of general lack of specific signs or symptoms. Hemorrhage is mainly intra-alveolar, although associated interstitial findings are not rare. This entity probably is a terminal event in most cases. When seen in term births, it is usually as a complication of other pathological states. Gross evidence of respiratory tract bleeding occurs in a significant proportion of these cases.

Mikity-Wilson syndrome, although also an interstitial process, is not usually seen in the immediate newborn period. With few exceptions, it occurs in prematures and has other clinical manifestations that should serve to differentiate it from congenital pulmonary lymphangiectasis.

Summary

Congenital pulmonary lymphangiectasis, although a rare anomaly, has characteristic clinical and radiological patterns which distinguish it from other causes of neonatal distress.

Radiological finding of a diffuse interstitial process in a newborn with profound cyanosis permitted a diagnosis of congenital pulmonary lymphangiectasis in the case reported.

REFERENCES

1. Virchow, R.: *Gesammelte Abhandlungen zur wissenschaftlichen Medicin*, Vol. 1, p. 1024, Frankfurt a.M., Meidinger, Sohn u. Co., 1856.
2. Fronstin, M. H., Hooper, G. S., Besse, B. E., and Ferreri, S.: Congenital pulmonary cystic lymphangiectasis. Case report and a review of 32 cases, *Amer. J. Dis. Child.*, 114:330-335, 1967.
3. Brown, M.D., and Reidbord, H. E.: Congenital pulmonary lymphangiectasis, *Amer. J. Dis. Child.*, 114:654-657, 1967.
4. Giedion, A., Müller, W. A., und Molz, G.: Angeborene Lymphangiektasie der Lungen. Eine radiologisch erkennbare Ursache des Atemnotsyndroms beim Neugeborenen, *Helv. Paediat. Acta*, 22:1-133, 1967.
5. Singleton, E. B.: Respiratory distress syndrome, *Progr. Pediat. Radiol.*, 1:109-134, 1967.
6. Theros, E. G.: An exercise in radiologic-pathologic correlation, *Radiology*, 89:524-531, 1967.
7. Carter, R. W., and Vaughn, H. M.: Congenital pulmonary lymphangiectasis. Report of a case with roentgen findings, *Amer. J. Roentgen.*, 86:576-578, 1961.
8. Frank, J., and Piper, P. G.: Congenital pulmonary cystic lymphangiectasis, *JAMA*, 171:1094-1098, 1959.
9. Heumann, G., Korn, R., et Levy-Silagy, J.: A propos d'un cas de lymphangiectasies pulmonaires congenitales, *Arch. Franc. Pediat.*, 17:1012-1023, 1960.
10. Javett, S. N., Webster, I., and Braudo, J. L.: Congenital dilatation of the pulmonary lymphatics, *Pediatrics*, 31:416-425, 1963.
11. Laurance, K. M.: Congenital pulmonary cystic lymphangiectasis, *J. Path. & Bact.*, 70:325-333, 1955.
12. Le Tan-Vinh, Cochard, A. M., et Vut Trieu Dong: Lymphangiectasies pulmonaires congenitales et lymphangite pleuro-pulmonaire cancéreuse métastatique de l'enfant, *Arch. Franc. Pediat.*, 21:165-182, 1964.
13. Tucker, A. S.: Lymphangiectasis: Benign and malignant, *Amer. J. Roentgen.*, 91:1104-1113, 1964.
14. Laurence, K. M.: Congenital pulmonary lymphangiectasis, *J. Clin. Path.*, 12:62-69, 1959.
15. Giammalvo, J. T.: Congenital lymphangiomatosis of lung: form of cystic disease; report of case with autopsy findings, *Lab. Invest.*, 4:450-456, 1955.

Gonadotropins: Present Concepts in the Human

R. S. SWERDLOFF, M.D., AND W. D. ODELL, M.D., PH.D., *Torrance*

GONADOTROPINS ARE CARBOHYDRATE-containing polypeptide hormones whose primary actions are to stimulate gonad and gamete growth and development and to increase steroid hormone secretion. Gonadotropins are secreted by the pituitary of all vertebrate species. The *pituitary* gonadotropins are three in number: (1) Luteinizing hormone (LH), or interstitial cell stimulating hormone (ICSH); (2) Follicle-stimulating hormone (FSH); (3) Prolactin or luteotropic hormone. This hormone is a gonadotropin in rats, but as yet is not known to function as such in humans. *Non-pituitary* sources of gonadotropins are rare. In higher primates and in humans trophoblastic cells of the placenta secrete a gonadotropin called chorionic gonadotropin. In pregnant mares (horse, donkey or zebra) endometrial structures called endometrial cups elaborate a gonadotropin which is harvested in serum and called pregnant mare's serum (PMS). Trophoblastic tumors and certain rare non-trophoblastic neoplasms of the human are also capable of elaborating a gonadotropin.¹

The gonadotropic hormone era was pioneered by a remarkably able group of investigators. Their discoveries laid the foundation for our current understanding of reproductive physiology. Some of the historical landmarks would include: the observation that hypophysectomy resulted in gonadal atrophy in dogs by Crowe and coworkers

in 1910,² followed by the discovery of luteinizing effects of hypophyseal tissue by Evans in 1921.³ In 1926 Zondek⁴ and Ascheim⁵ described the presence of gonad-stimulating hormones in the human hypophysis. These same men presented evidence in 1927⁶ and 1930⁷ that the urine of pregnant women contained a gonad-stimulating factor separate from that found in the urine of postmenopausal women.

Smith and Engle⁸ demonstrated in 1927 that gonadal atrophy developed in hypophysectomized rats. Evans and Simpson's studies⁹ in 1928 and those of Weisner and Marshall in 1931¹⁰ indicated that at least two pituitary gonadotropic hormones existed. Fevold, Hisaw and Leonard fractionated pituitary gonadotropin extracts into LH and FSH.¹¹ Moore and Price proposed a feedback control system for gonadotropin in 1932.¹² Klinefelter and coworkers described the assay of human urinary gonadotropins.¹³ The role of the hypothalamus was firmly established in 1952 when Harris and Jacobson¹⁴ demonstrated that immature rat hypophyses transplanted under the median eminence of hypophysectomized adult female rats restored vaginal cytology and supported mating, pregnancy and delivery of normal young.

In 1940 Li and coworkers¹⁵ and Shedlovsky and associates¹⁶ reported the partial purification of LH. In 1949, Li¹⁷ reported the partial purification of FSH. Recent technological advancements in the measurement of polypeptide and steroid hormone have led to a new era of understanding in reproductive physiology. The availability of highly purified gonadotropins¹⁸⁻²¹ and the applica-

From the Department of Medicine, Harbor General Hospital, Torrance, and UCLA School of Medicine, Los Angeles.

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Reprint requests to: Endocrinology Division, Harbor General Hospital, 1000 West Carson Street, Torrance 90509 (Dr. Swerdloff).

tion of the radioimmunoassay methods have allowed quantification of the small concentration of hormones present in normal plasma and serum. This paper will attempt to review the nomenclature, biochemistry, bioassay and immunoassay systems used for quantification of hormone concentration, and to describe our current concepts of gonadotropin physiology. The discussion is directed toward human physiology, but pertinent studies in animals are discussed.

Nomenclature and Chemistry

Follicle Stimulating Hormone (FSH). This is the pituitary hormone which stimulates growth of the ovarian follicle and may participate in ovulation in women. In men it causes growth of the seminiferous tubule and maintains spermatogenesis. Human FSH (HFSH) has been shown to have a molecular weight of about 30,000 to 45,000.^{22,23} The amino acid sequence is not known but the proportion of individual amino acids present has been determined for several human pituitary FSH preparations.^{23,24} These studies indicate a carbohydrate content of approximately 20 percent. In the preparation studied by Amir and Somers,²⁴ carbohydrates consisted of galactose, mannose, glucosamine, fucose and ascorbic acid (N-acetyl-D-neuraminic acid). Reichert and coworkers²³ reported an average of 5 percent sialic acid, 12 percent hexose (mannose) and 9 percent hexosamine in two separate preparations studied.

Luteinizing Hormone (LH) or Interstitial Cell Stimulating Hormone (ICSH) is the pituitary hormone which is responsible for inducing ovulation and transforming the follicle remnant into a functioning corpus luteum. In males it acts to stimulate the interstitial cells to secrete testosterone. Jirgensons reported it to be a globular glycoprotein with little or no alpha helix structure.²⁵ The molecular weight of human LH has been estimated to be between 25,000 and 45,000.^{22,23,26,27} The amino acid composition of human LH has been determined by Li²⁶ and Kathan and coworkers.²⁸ The studies of Kathan and associates²⁸ indicated a lower content of both sialic acid and hexosamine in HLH suggesting it is a less acidic protein than HFSH.

Human Chorionic Gonadotropin (HCG) is secreted by the *placental* trophoblastic cells. It is felt to be necessary for the maintenance of the corpus luteum of pregnancy and the secretion of estrogen and progesterone from that site. HCG is very similar to LH in immunologic and biologic

properties but does differ in some aspects of its chemical characterization. The isoelectric point for HCG (pH 2.95) is lower than that reported for LH and other pituitary glycoproteins.^{26,29,30} There is some indication that its carbohydrate content is less than that of LH and that it contains a lower proportion of sialic acid. The molecular weight has been estimated to be 30,000 by light scattering and ultracentrifugation³¹ and by radiation inactivation.³² A similar hormone (a tumor gonadotropin) is present in blood and urine of patients with certain trophoblastic tumors (for example, choriocarcinoma) and in rare instances in patients with non-trophoblastic malignant lesions (such as carcinoma of the lung and hepatoblastomas).³³

Pregnant Mare's Serum Gonadotropin (PMS) was first described in 1930 by Cole and Hart.³⁴ This material behaves in bioassays like a mixture of LH and FSH.³⁵ Its importance in the human is its use as a form of gonadotropin treatment.

Assay Systems and Reference Preparation

The gonadotropic hormones LH, FSH and HCG can be currently quantified by determining either the biologic or immunologic effect of a given specimen. Thus, assay systems for these hormones can be divided into immunoassay and bioassay techniques. The methods available with their limitations and advantages will be discussed below. It is not the purpose of this discussion to present detailed principles of bioassay or immunoassay, but understanding current physiology requires a general familiarity with these principles. The reference or standard preparations used to express potencies are particularly confusing to the student of gonadotropin physiology.

In early publications, investigators often stated potencies in terms of a bioassay response. For example, the amount of gonadotropin required to double the weight of the uterus in immature mice was a "mouse uterine weight unit." As experience increased, the variability in such responses from laboratory to laboratory or even in the same laboratory from time to time led to the use of reference or standard gonadotropin preparations. A large supply of an easily obtainable gonadotropin was accumulated and this was simultaneously assayed with the unknown preparations. It was hoped that in this manner, different investigators using different bioassays could directly compare data. As will be seen, the exact nature of the reference preparation must be stated.

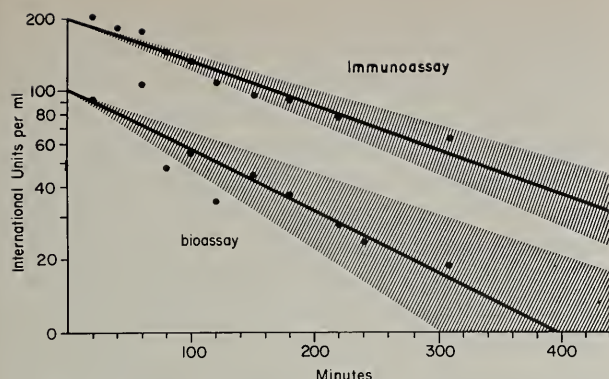


Figure 1.—Disappearance of human LH from the plasma of a dog after a single intravenous injection. The 2nd IRP was used as a reference preparation and plasma samples obtained at the indicated times were assayed by bioassay and by radioimmunoassay. The bioassay used was the ventral prostate weight increment in hypophysectomized immature male rats. The dark lines indicate the calculated slope of disappearance for immunoassay (top) and bioassay (bottom). The shaded areas indicate the 95 percent confidence limits at these slopes. Note that the slopes of disappearance are similar for both assay systems, that is, the relation of one plasma sample to another is similar, but *absolute* values are consistently higher for the radioimmunoassay. Reproduced with permission from Odell, Reichert and Swerdloff.³⁸

The first international standard for HCG was established in 1939; one International Unit (I.U.) was defined as the activity in 0.1 mg of the standard urinary material. The second international standard was made available in 1965.³⁶ It was concentrated and partially purified from urine and was assigned a potency for each ampoule (approximately 6.8 mg) of 5,300 I.U.

Reference preparations are also available as standards for the pituitary gonadotropins LH and FSH. The original international reference preparation was from the urine of postmenopausal women: the international reference preparation of human menopausal gonadotropin (IRP-HMG). This has now been replaced by a second reference preparation (2nd IRP-HMG), also an extract of postmenopausal human urine. This 2nd IRP-HMG contains both LH and FSH, and serves as reference for both hormones. It has been assigned a potency of 40 I.U./ampoule of each.

A number of animal LH and FSH preparations have been used as references for measuring human materials. Only recently has it become apparent that the *relative* potency of a human unknown stated in terms of an animal standard may vary with the bioassay used. Thus the ovarian ascorbic acid depletion assay (for LH and HCG) gives a potency of 1,538 I.U. per mg for the National Institutes of Health ovine LH preparation #S-1³⁷

(NIH-LH-S1), while the prostate weight increment assay gives a potency of 66.6 I.U. per mg.³⁷ With very rare exceptions, gonadotropins from non-human sources give no response in the radioimmunoassays. For all of these reasons, use of reference preparations from non-human sources to quantify human gonadotropins should be avoided.

To further complicate matters, questions have recently arisen as to the appropriateness of human urinary reference preparations to quantify human pituitary unknowns. Figure 1 and Table 1 illustrate this problem. When potency estimates are determined for human pituitary preparations using a urinary reference preparation, the immunoassay consistently gives higher values.³⁸ Without going into detail, it does not appear that this observation can be explained by the hypothesis that the immunoassay measures biologically inactive, immunologically potent fragments. For a more complete discussion, the reader is referred to earlier publications.^{38,39} Relative potencies of one human pituitary material to another human pituitary material are correctly assigned by both bioassays and immunoassays. The correct reference preparation for serum or plasma remains unknown.

While all this may confuse the novice gonadotropin physiologist, he may be reassured that it often confuses even the so-called experts. As was stated, however, the introduction of reference preparations represented a major advance. The reader and student should always carefully record which reference preparation is used. For the present, and in the near future, the 2nd IRP-HMG will be used most commonly for human LH and FSH, and the international preparation of HCG will be used for HCG. Note that the I.U. of LH and FSH,

TABLE 1.—Bioassay-Immunoassay Potency Estimates of Pituitary HLH Preparations

Pituitary Preparation	Potency by OAAD Bioassay* I.U./mg	Potency by Radioimmunoassay I.U./mg	Relative Potency OAAD Bioassay*	Relative Potency Radioimmunoassay
A	126.1	232.3	1	1
B	2,614.0	11,453.0	20.7	49.1
C	1,476.0	2,834.0	11.7	12.1
D	569.0	2,466.0	4.5	10.6
E	61.5	263.0	0.49	1.02
F	4,599.0	10,506.0	36.5	44.7
G	169.2	1,227.0	1.3	5.3
H	231.0	940.0	0.09	0.51
I	431.0	1,364.0	1.8	4.2
J	3.4	5.9

*Ovarian ascorbic acid depletion bioassay. From: Parlow (1961). NIH-S1-LH was used as a standard and converted to I.U. by multiplying by 1,538 (Reichert, 1967).

TABLE 2.—*Approximate Translation* Values for Various Gonadotropin Units*

10 mouse units (MU) HCG	= 1 International Unit (I.U.) HCG
1 I.U. HCG	= 0.8† I.U. LH
1 mg NIH-FSH-S1	= 26.5 I.U. 2nd IRP (AR)†‡§
1 mg NIH-LH-S1	= 51.3§-66.6‡ I.U. 2nd IRP (VPW)
1 mg NIH-LH-S1	= 588§-1538†‡ I.U. 2nd IRP (OAAD)

*The translation values from NIH-LH-S1 to the 2nd IRP-HMG in the OAAD assay are complex. Published values are in the range given. Frequently, the 2nd IRP does not give a parallel dose response to the NIH-LH-S1 in this assay, possibly because high doses of the latter are toxic to the rats (Dr. L. E. Reichert, personal observations). However, strain differences in rats used for assay cannot be excluded.

†Reference 30.

‡Reference 37.

§Reference 40.

and HCG are different. Table 2 represents the best available translation values for the standards or reference preparations used in gonadotropin assays.

Gonadotropin Bioassays

Until very recent times bioassays were the only available means to quantitate the gonadotropic hormones. A number of specific and non-specific systems are available. The specificity and sensitivity of some of these bioassays are presented in Table 3. The earliest techniques were quite non-

specific but improved methodology resulted in specific bioassays for LH and FSH. The major difficulty with these specific systems is their lack of sensitivity. It can be seen from the data in Table 3 that the minimal detectable quantity in a 24-hour unconcentrated urine is equivalent to about 50 I.U. (IRP-HMG #2). This value is about four times the normal urine value in men and in eugonadal women (at all times other than the midcycle peak). Because of this insensitivity, quantitation of gonadotropins in eugonadal subjects by bioassay requires concentrations of 24-78 hour urine specimens. Even 24-hour collections of urine from normal men and women may be inadequate for precise quantitation.

Regarding the individual tests, several points are worth presenting. The *mouse uterine weight test*¹³ is widely used as a clinical measurement of "total urinary gonadotropins." It is not specific for LH, FSH, or HCG and is sometimes incorrectly referred to as an FSH assay. The ratio of LH to FSH in a urine specimen has been shown to influence the uterine weight response.⁴⁰ It is the most sensitive of the well-established bioassay techniques (detecting as little as 80-100 mI.U. 2nd IRP) and is usually satisfactory to distinguish primary *hypogonadism* (urinary gonadotropin excretion high) from pituitary *hypogonadotropism* (urinary excretion low). However, great overlap exists

TABLE 3.—*Methods of Bioassay*

Bioassay	Specificity	Sensitivity*		Amount Injected Per Animal	Minimal Detectable Amount In Unconcentrated Urine I.U. 2nd IRP†
		HCG	2nd IRP		
Mouse Uterine Weight	FSH, LH, HCG	0.1	0.08	1.5 - 2.5	48
Rat Uterine Weight	FSH, LH, HCG	0.25	0.20	4	75
Rat Prostate Weight	LH, HCG	0.25	0.20	4	75
Rat Ovarian Ascorbic Acid Depletion	LH, HCG	0.5	0.4	2§	300
Mouse Ovarian Ascorbic Acid Depletion	LH, HCG	0.25-0.75	0.2-0.6	0.2	1,500 - 4,500
Rat Ovarian Hyperemia	LH, HCG	0.5	0.4	2	300
Rat Testis Weight	FSH, LH,¶ HCG	..	1.0	4	375
Rat Ovarian Cholesterol Depletion	LH, HCG	.00006	.00005‡	0.5	0.02
Mouse Ovarian Weight Augmentation	FSH, ?	..	0.25	2.5	150
Rat Ovarian Weight Augmentation	FSH	..	1.0	4	375
Frog Spermination	FSH, LH, HCG	5	4	2	3,000

*Sensitivity is defined as minimal effective dose. This is not the working range of the assay but rather the point where the dose response curve crosses the control response line. The sensitivities of all assays vary from laboratory to laboratory and with the strain of animals used.

†In measuring the detectable amount in unconcentrated urine, it was assumed that the 24-hour urine volume was 1,500 ml. The normal amount is less than 20 I.U. HCG.

‡This assay is extremely sensitive. However, there is a peculiar biphasic characteristic to the dose response curve which makes this assay of limited practical value.

§2 ml is theoretical as raw urine is toxic to the rat in this assay.

¶Predominantly LH, HCG.

TABLE 4.—*Gonadotropin Levels in 110 Consecutive 24-hour Urine Specimens from Two Menstruating Women*

Patient	Days	Mouse Uterus Units*				
		10	10-50	50-200	200-500	500
	No.	%				
J. M.	56	11	63	20	4	2
C. F.	54	18	48	24	8	2
Average . .		15	77		8	

*One mouse uterus unit = 0.1 I.U. human chorionic gonadotropin.

between normal and abnormal values. An example of the difficulty in using this assay in clinical situations is shown in Table 4. In this study⁴¹ 110 consecutive specimens of urine from two normally menstruating women were assayed by the mouse uterine weight method. The normal range for eugonadal women was 1 to 20 I.U. 2nd IRP. Note that 15 percent of the time the gonadotropins were undetectable while 8 percent of the time they were in the range usually encountered in castrate or postmenopausal women. The *rat uterine weight assay* is also nonspecific and is less sensitive than the mouse assay.

There are a number of bioassays which have been prepared to be specific for LH. Two have gained widespread acceptance and use: the *ventral prostate weight assay* (VP) and the *ovarian ascorbic acid depletion assay* (OAA). The VP assay was described by Greep and coworkers⁴² 27 years ago, and is performed on immature, hypophysectomized or intact rats injected over a four-day period; the ventral prostate weight is determined on the fifth day. The OAA was described by Karg in 1957⁴³ and by Parlow in 1961⁴⁴ and has the advantage of being a one-day assay in which the depletion of ovarian ascorbic acid is determined in PMS-HCG primed, immature rats. A number of modifications have been proposed for the OAA. Among those reported are the age of rats,⁴⁵ the amount and time interval between PMS and HCG injections,⁴⁶ the mode of injections,⁴⁷ the use of mice instead of rats,⁴⁸ and the measure of cholesterol instead of ascorbic acid.⁴⁹

Several other assays are used to quantitate LH: The *rat ovarian hyperemia assay* has been shown to be relatively specific⁵⁰ and is slightly less sensitive than the methods above. A *mouse ovulation assay*,⁵¹ based on the induction of ovulation in mice pretreated with PMS, is not specific for LH.⁵² The *rabbit ovulation* system is very insensitive and appropriate only for pregnancy testing.

The one method universally stated to be specific for FSH depends on the increase in ovarian weight

of immature rats treated with an excess of HCG.⁵³ The assay is known as the *ovarian augmentation assay* (AR). The same assay performed in the mouse is more sensitive⁵⁴ but may not be specific for FSH.⁵⁵ Efforts have been made to develop more sensitive FSH bioassays. Igarashi and McCann⁵⁶ reported a highly sensitive method using an augmentation of uterine weight in HCG treated mice. The specificity of this method, however, has been challenged by Ross and Brown⁵⁷ who demonstrated that LH interfered in the response.

Radioimmunoassays

A major technological advance in hormone measurement occurred in 1960 when Yalow and Berson⁵⁸ described the radioimmunoassay of plasma insulin. One year later, Wide⁵⁹ described an agglutination immunoassay for HLH based on the cross-reaction of HLH with antibodies directed against HCG. In 1964 Paul and Odell first described a radioimmunoassay for HCG.⁶⁰ When in 1966 a purified preparation of HLH suitable for iodination became available, Odell and coworkers,⁶¹ Midgley⁶² and Franchimont⁶³ applied this technique to the measurement of HLH in serum. The following year, Odell and Parlow,⁶⁴ Midgley,⁶⁵ Faiman and Ryan⁶⁶ and Franchimont⁶³ reported on successful radioimmunoassay methods for HFSH. At present, radioimmunoassay measurements are commercially available for LH and HCG.

Because of the immunologic and biologic similarities of the two hormones, LH and HCG are not distinguishable from each other in any currently available system. Thus, LH cannot be measured in a pregnant woman. The radioimmunoassay for FSH is only available in certain research centers at this date, but undoubtedly will become generally available in the near future. Prolactin immunoassays are in the developmental stage. The effect of the availability of radioimmunoassay is apparent when one realizes that those methods are not only specific, but are 150 to 500 times more sensitive and simpler to perform than bioassay methods. LH and FSH can be quantified in 0.1 to 0.4 ml of serum from eugonadal subjects.

A brief description of the method of the radioimmunoassay (RIA) will be presented. In the radioimmunoassay system (Figure 2) plasma containing an unknown amount of hormone is added to a known amount of radioiodine-labeled hormone. Both are incubated with antiserum containing antibodies which combine specifically with the

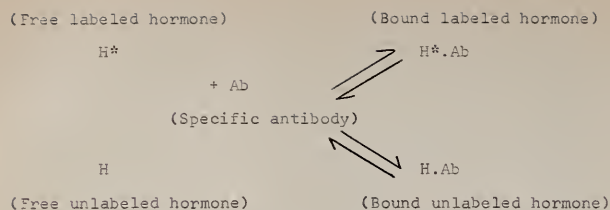


Figure 2.—Simplified scheme of radioimmunoassay system, demonstrating the competition of labeled hormone (H*) and unlabeled hormone (H) (in serum, urine, or standard) for a specific antibody (Ab).

hormone being tested. The unlabeled and labeled hormones compete for the binding sites of the antibody. The antibody-bound hormone is then separated from the unbound by any of several methods.⁶⁷ The amount of radioactive hormone that is antibody-bound and the amount that is free (unbound) are determined in a gamma counter. The more unlabeled hormone present, the more labeled hormone will be displaced from the antibody. Serum hormone concentration is determined by comparing the proportion of bound to free radioiodine-labeled hormone in the assayed samples to a standard curve in which known amounts of hormone were used instead of serum specimens.

The specificity of the radioimmunoassay is dependent on the specificity of the antisera used. LH, FSH, HCG and thyrotropin (TSH) are all carbohydrate-containing hormones having similar molecular weights, and having similar biochemical and immunological properties. Preparing antisera

specific for one hormone is often a difficult task. Specificity must be rigorously tested for every antiserum. Note that specificity does not imply that the antiserum contains only antibodies directed against one hormone (for example, FSH), but that the antibodies that are directed against FSH are not directed against the immunologic portions of FSH also shared by LH or TSH. Only antibodies binding radioactive FSH are used. Displacement of antibody-bound FSH must occur with FSH only and not with LH, HCG or TSH. Figure 3 demonstrates two antisera obtained in different bleedings from the same rabbit which had been injected with impure FSH. The curve on the right demonstrates almost complete cross reactivity: LH and FSH produce almost identical dose responses. Therefore, using such an antisera, one could not distinguish LH and FSH in a serum specimen. The curve on the left demonstrates very little cross reaction between LH and FSH. The dose response curve for LH is very flat; and only FSH would be measured in the assay. This latter antisera would be satisfactory for use in an hFSH assay.

Figure 4 depicts radioimmunoassay dose response curves for purified LH, for an extract of postmenopausal urine (pergonal) and for serum from a postmenopausal woman. The entire dose response curve was obtained with use of less than 1 ml of serum. Note also the precision possible with this assay system.

These remarks are not intended to imply that

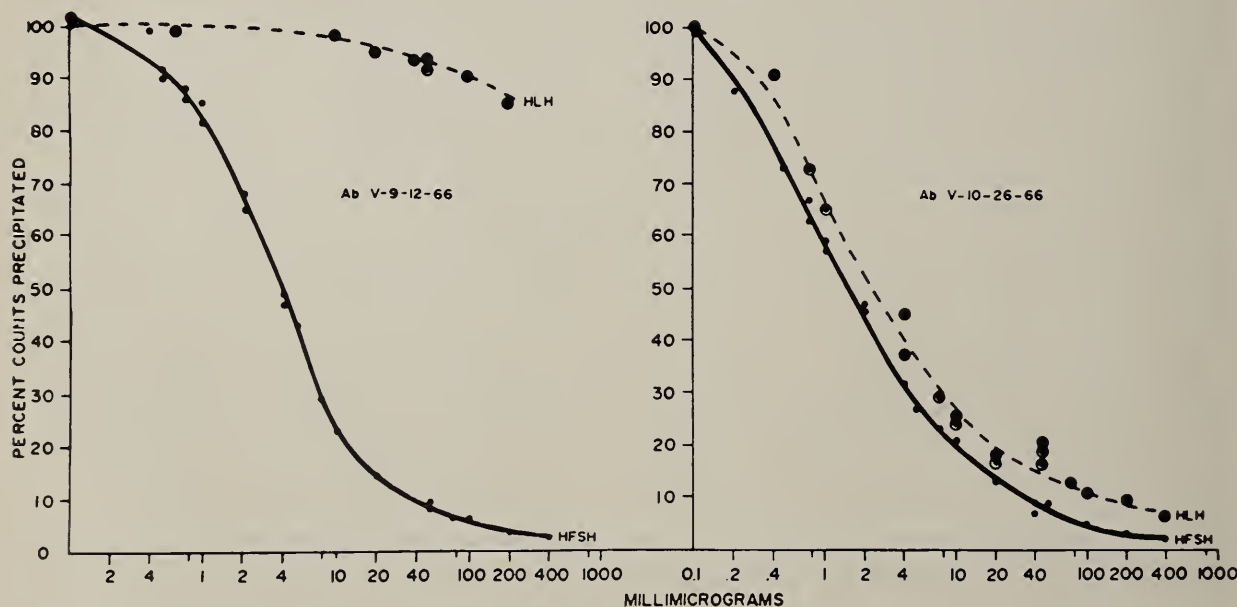


Figure 3.—Radioimmunoassay for human FSH using two antisera obtained from the same rabbit at different times. That on the left was fairly specific for FSH; LH showed little cross reaction. That on the right was completely non-specific; LH, and FSH both gave equal reaction. Reproduced with permission from Odell, Reichert and Bates.³⁹

RADIOIMMUNOASSAY HLH

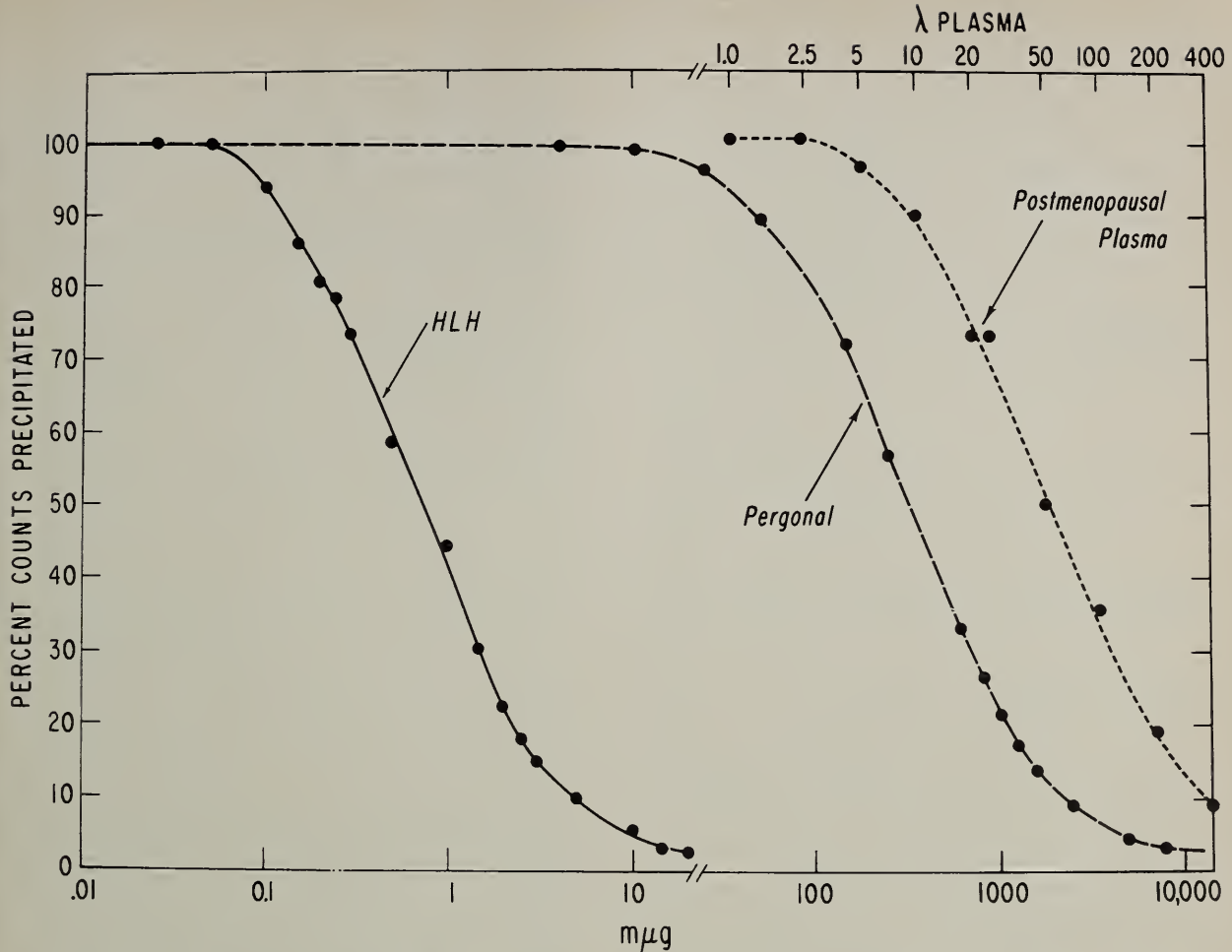


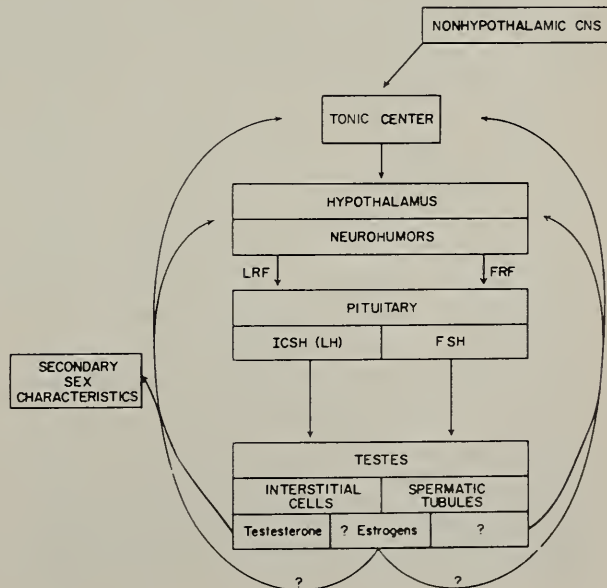
Figure 4.—Dose response curves for highly purified human LH (HLH), for an extract of postmenopausal urine (pergonal) and for plasma from a postmenopausal woman. The entire dose response curve for plasma was made with less than one ml.

radioimmunoassay procedures are problem-free. Many difficulties exist, and for the interested reader additional references are given throughout this manuscript.

Physiologic Considerations

Although numerous observations and facts have been gathered concerning the physiology and control mechanisms of gonadal function, knowledge of this subject remains amazingly incomplete and fragmentary. Figures 5 and 6 present in diagrammatic form some of the factors involved in gonadal physiology in men and in women.

Figure 5.—Schematic presentation of the central nervous system-pituitary-testicular interrelations in men. Question marks indicate that the role or type of the hormone is uncertain. The "short loop" FSH and LH feedback loops observed in rats are not depicted. See text for discussion.



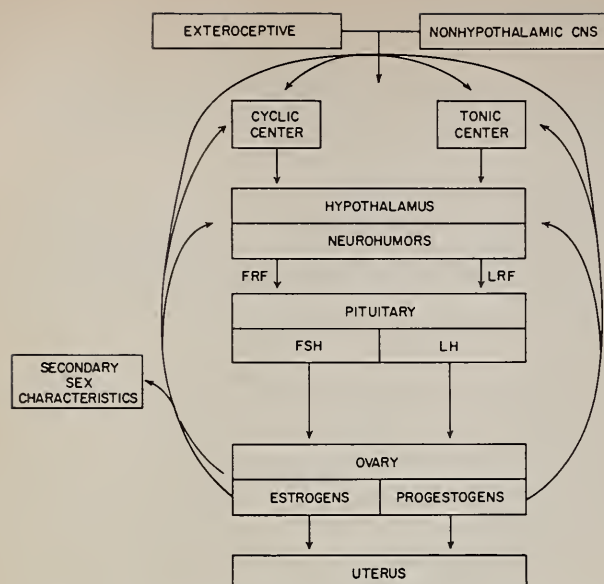


Figure 6.—Schematic presentation of the central nervous system-pituitary-ovarian interrelations in women.

Central Nervous System Pituitary Interrelationships

It is now known that the synthesis and release of LH and FSH by the pituitary is regulated by centers in the hypothalamus.⁶⁸ These centers produce their effects by means of neurohumoral substances (releasing factors) secreted into the hypothalamic pituitary portal vascular system. Two separate substances, LH-releasing factor (LRF) and FSH-releasing factor (FRF) have been identified from hypothalamic tissue and measured in blood.⁶⁸ While there is no doubt that these releasing factors exist and are of paramount importance in controlling pituitary LH and FSH secretion, their chemical identity is uncertain. Early studies by Guillemin and coworkers⁶⁹ and Ramirez and McCann⁷⁰ suggested that they were small polypeptides (molecular weight 1,000 to 5,000). However, recent studies⁷¹ and further purification attempts have led to some doubt as to their structure. At present, one can only state that they appear to be relatively small chemical substances capable of specifically releasing FSH or LH from pituitary tissue.

In the female rat, several specific areas of the hypothalamus are involved in the control of LH secretion.^{72,73} The first level of hypothalamic control involves the "tonic" discharge of gonadotropin in sufficient quantity to maintain estrogen production. The classic feedback between blood estrogen levels and LH secretion exists in rats. This tonic center cannot independently initiate the preovula-

tory surge of gonadotropin responsible for normal female cyclicity. In rats, the tonic center appears to be located in the region of the arcuate-ventromedial nucleus. A second higher center (cyclic center) appears to exist in the preoptico supra chiasmatic region and is responsible for the cyclic discharge of LH resulting in ovulation. Appropriate function of the cyclic center is dependent on an intact tonic center. Tiny destructive lesions produced in the tonic center result in loss of both tonic control and cyclic gonadotropin release. Unlike female rats, male rats do not have an active cyclic center. In both sexes, the hypothalamus appears to be undifferentiated in this regard at birth⁷⁴ having the potential to cause cyclic release of gonadotropin on maturation. Intact testes in males or androgen administration to either sex during the neonatal period results in a loss of later gonadotropin cyclicity.^{72,75} While either androgen administration or androgen production from the testes prevents hypothalamic cyclicity in mice and rats, this is not known to be true in other mammalian species or in humans.

Childhood and Puberty

Until the last two or three years, it was generally believed that before puberty children excreted no gonadotropin in urine and had none circulating in blood. Puberty was believed to be caused by the onset of pituitary gonadotropin secretion.⁷⁶ In 1967, Odell, Ross and Rayford⁷⁷ reported that, using their radioimmunoassay for LH, this gonadotropin was detectable in serum for all children over the age of one (see Table 5). With this observation as impetus, and studying large amounts of urine, further studies from the same laboratory revealed bioassayable amounts of total

TABLE 5.—Normal Values for HLH and HFSH

Gonadal Status	Sex	HLH (mI.U./ml*)	HFSH (mI.U./ml*)
Eugonadal Adult . .	Male	6-30	5-25
Castrate	Male	40-100	> 30
Prepubertal†	Male	4-16	< 5
	Female		
Eugonadal Adult			
Follicular Phase . . .	Female	6-30	7-21
Luteal Phase	Female	5-20	5-15
Midcycle Peak	Female	40-160	15-32
Castrate or			
Postmenopausal . . .	Female	40-210	40-250

*Milliunits of the Second International Reference Preparation (IRP-HMG#2) kindly supplied by the Medical Research Council, Mill Hill, London.

†Age one or more.

gonadotropins⁷⁸ and specifically LH and FSH⁷⁹ in urine from prepubertal children.

Other investigators,^{80,81} using LH immunoassays, have also found that LH was present in serum from prepubertal children. These data indicated that in children, puberty is not merely the onset of gonadotropin secretion by the pituitary. For investigators familiar with studies in rats, this was not surprising. In 1929 Kallas⁸² reported that if two prepubertal rats were joined in parabiosis and one castrated, the other underwent precocious puberty, suggesting that a dynamic pituitary-gonadal relationship had been disturbed. In 1951 Byrnes and Meyer⁸³ demonstrated that tiny doses of estrogen, too small to stimulate uterine weight, administered to the castrate partner would prevent this precocious puberty. Unfortunately most clinicians were unaware of these studies.

While the precise stimuli for the initiation of puberty in males and females are still unknown, some hypotheses have been advanced. The demonstration that the hypothalamic pituitary system in immature rats is more sensitive to the inhibitory effects of gonadal steroids than that of adults^{12,83-85} has led to the suggestion⁸⁶ that the onset of puberty might be determined by a shift in the threshold of the steroid-gonadotropin negative feedback mechanism at the time of puberty. This would lead to an *increased* gonadotropin secretion which would in turn result in puberty. Other investigators⁸⁷ have noted that low dose estrogen administration to rats can induce precocious puberty. The site of this positive feedback mechanism appears to be the preoptic region of the hypothalamus.⁸⁸ Thus, it has been postulated that, in females, gonadal steroids slowly increase under low grade LH and FSH stimulus until they reach the threshold level of the hypothalamic cyclic center which then triggers off the first ovulatory upsurge in LH release.

Another possible mechanism of prepubertal LH-FSH suppression was suggested when Morrison and Johnson⁸⁹ and later Pincus⁹⁰ reported the finding of gonadotropin-inhibiting factors in the hypothalamus. These inhibitors have been found in the hypothalamus of infants and prepubertal children, suggesting that they may be involved in holding the pituitary-gonadal circuit in check until puberty.⁹¹

Gonadotropins in Men

Daily serum LH and FSH concentrations are higher following puberty in men. They remain constant from day to day, however, in contrast to

a pronounced cyclicity in women. The normal range is presented in Table 5. The possibility of a diurnal variation of these hormones has been investigated by us and by others. Most studies have failed to demonstrate any such change for LH.^{77,92-94} The data for FSH are less clear. Several laboratories have reported significantly lower P.M. than A.M. values.^{81,95} Others,⁹³ ourselves included,⁹² have not been able to document such a change. Furthermore, we have not noted a change in LH or FSH in relationship to severe exercise, ingestion of a meal or carbohydrate load, infusion of arginine, injection of vasopressin or during surgical stress.⁹²

The current concepts of feedback control of gonadotropin secretion in men are depicted in Figure 5. The most acceptable concept is as follows: LH stimulates the interstitial cells of the testes to secrete testosterone which, in turn, acts as an inhibitor of LRF release and therefore of further LH release. FSH primarily stimulates the growth and development of spermatogenic tissue which in turn is thought to secrete an unknown

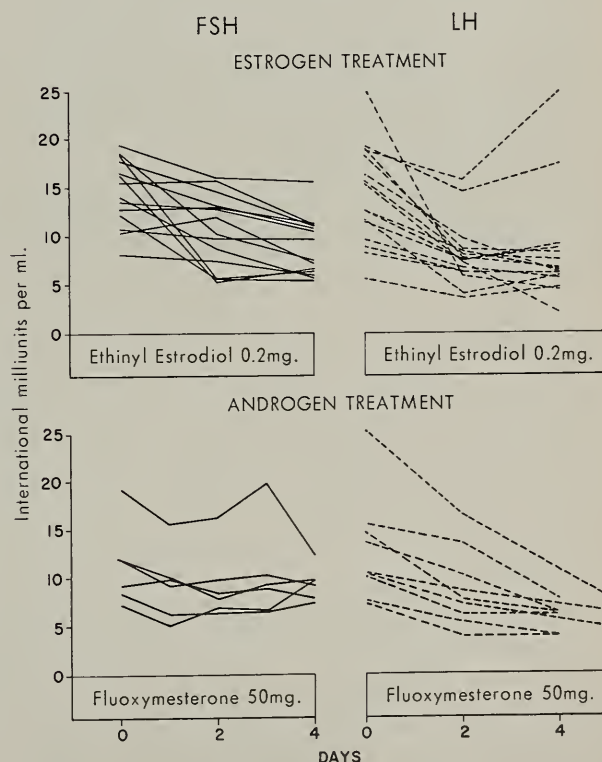


Figure 7.—The effects of estrogen and high doses of androgen on serum FSH and LH concentrations in eugonadal men. Ethinyl estradiol suppressed both LH and FSH; fluoxymesterone, 50 mg per day and at 10 mg per day (not shown), suppressed LH but failed to affect FSH. Reproduced with permission from Swerdloff and Odell, (Lancet, in press).

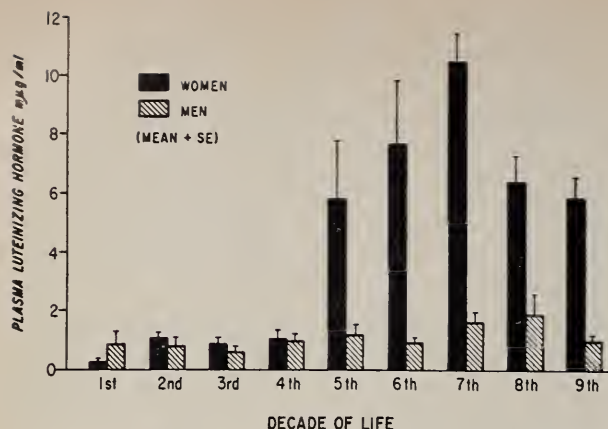


Figure 8.—Plasma luteinizing hormone concentrations in men and women of different ages. Reproduced with permission from Schalch et al.⁸⁰

factor which inhibits FSH release (presumably acting again at hypothalamic level). These concepts are based on the following data: the loss of both spermatogenic and Leydig cell function such as occurs after castration in man results in elevation of both serum LH and FSH.⁹⁶ Administration of testosterone to castrated rats (and presumably to men) results in a fall of LH levels toward normal.⁹⁷ Selective loss of *spermatogenic tissue* (interstitial cell activity normal) produced by testicular irradiation in men results in elevations of FSH⁹⁸; LH levels remain normal. Treatment of eugonadal men with androgen (Figure 7) results in lowering of serum LH but not of FSH.⁹²

Some investigators^{99,100} have postulated that the germinal epithelium secreted a non-androgenic,

non-estrogenic water-soluble material which they designated "inhibin." Inhibin would then circulate in plasma and act as an inhibitor of FSH synthesis and release. Johnsen¹⁰¹ has suggested that the source of this germinal hormone is the cytoplasm lost at the final stage of spermatoid development (residual body). These residual bodies have been shown to be phagocytized by the Sertoli cells. This theory remains unproved. Others have postulated that the testis, perhaps the Sertoli cells, produce an estrogenic substance which controls FSH secretion.¹⁰² This is consistent with the finding that estrogen treatment (Figure 7) will suppress both serum LH and FSH in eugonadal males.⁹² The finding of elevated FSH in patients with normal appearing Sertoli cells and absent germinal tissue (Sertoli-only syndrome) has been used as an argument against this theory.¹⁰³

Castrated males have elevations of LH and FSH similar to that of postmenopausal and castrated females (Table 4). While male menopause does not seem to exist as a well defined state, there is evidence⁸⁰ that LH increases progressively with increasing age (Figure 8). Presumably this reflects decreasing feedback inhibition from gonadal androgens.

Gonadotropins in Women

Unlike the male, the eugonadal female has fluctuations in serum LH and FSH which correspond to specific periods during the menstrual cycle. Figure 9 is a schematic representation of serum

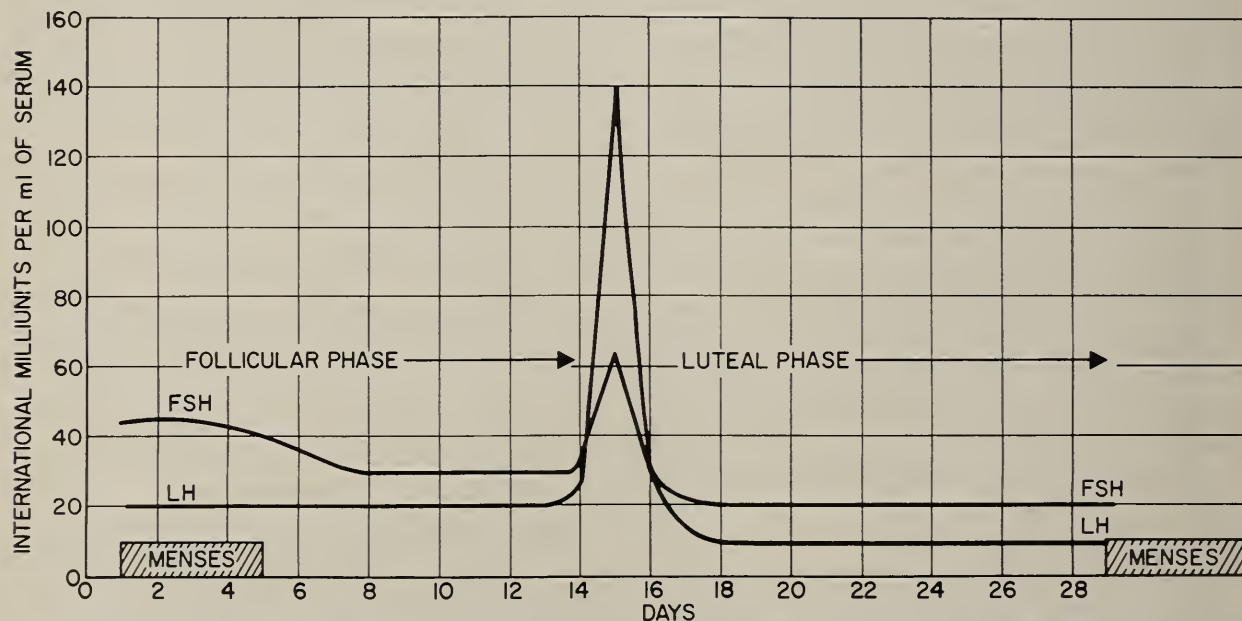


Figure 9.—Schematic presentation of the fluctuations in FSH and LH in serum throughout the menstrual cycle. Reproduced with permission from Odell and Swerdloff.¹¹⁵

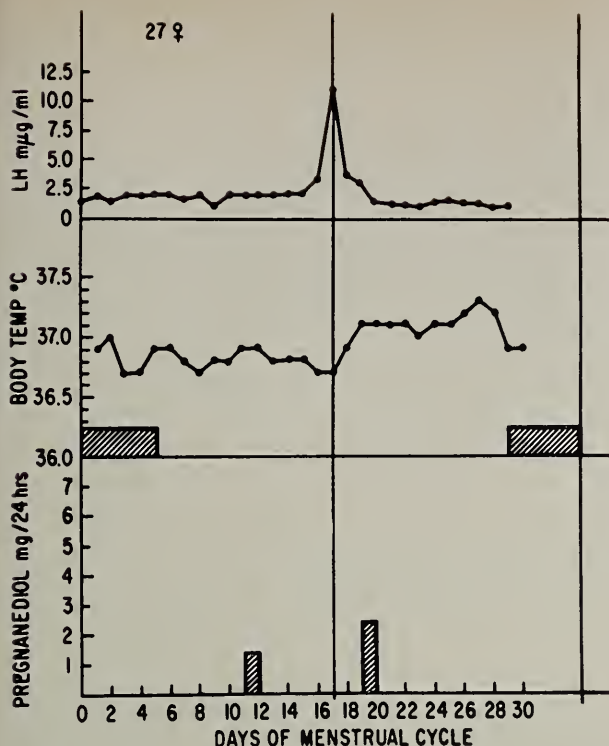


Figure 10.—Plasma LH levels measured daily throughout a menstrual cycle in a 27-year-old woman. Menstrual flow is shown by the shaded bars under the body temperature curve. Note the constancy of LH levels except at midcycle. Note also that mean LH levels during the follicular phase are higher than during luteal phase. Reproduced with permission from Odell et al.⁷⁷

concentrations of LH and FSH measured daily throughout the menstrual cycle. LH is seen to be fairly constant during the follicular phase (period of follicular growth before the increase in basal body temperature). A sharp peak in LH is seen which usually lasts about 48 hours (Figure 10). This LH peak is believed to cause ovulation. The range in the height of the LH peak is from 40 to 160 mIU. and has been seen to occur from 13 to 33 days after the onset of menses.^{96,104} We have not seen any women with well documented regular menstrual periods who have not had an LH peak. Following the LH ovulatory peak, and during corpus luteum function, LH concentrations fall to levels lower than during the follicular phase.

Serum FSH also fluctuates with the menstrual cycle^{63,66,81,105} (Figure 9). A midcycle peak in FSH smaller in height but corresponding in time and duration to the LH peak is seen in most subjects. This is preceded by a follicular phase during which an early elevation in FSH is seen. In our experience the magnitude of this elevation has been small, concentrations of FSH in the first half of the follicular phase being 10 percent higher than dur-

ing the second half. However, it is present in most individuals and is statistically significant for the group. Others have reported even higher early phase follicular levels.^{66,106} Luteal phase FSH levels are lower than follicular phase levels.¹⁰⁵ The role of the FSH midcycle peak in the production of ovulation is unknown. These radioimmunoassay studies of LH are consistent with earlier studies using bioassays and immunoassays on concentrates of 24-48 hour urines in which a midcycle elevation of HLH excretion was reported.¹⁰⁷⁻¹¹³ The urinary peak of HLH has in general been less striking or more blunted than that seen in blood. Bioassay studies of FSH in urine concentrates are more conflicting than the LH data. Fukushima and coworkers¹¹¹ and Stevens and associates,¹¹² for example, reported high FSH excretion during the late luteal and early follicular phase but no midcycle elevations. In contrast, McArthur and coworkers,¹⁰⁷ Buckholtz¹¹⁴ and Rosenberg and Keller¹⁰⁹ have found midcycle elevations of FSH excretion.

The presence of cyclic fluctuations of LH and FSH has increased the complexity of the *feedback control mechanisms* involved in female gonadotropin physiology. Evidence was presented above that the capacity for cyclic gonadotropin release is present at birth in female rats and that it manifests itself at the time of puberty. From that time forth, until the onset of the menopause, non-pregnant normal females possess some form of biologic clock producing regular fluctuations of hypothalamic and pituitary hormones which result in midcycle LH and FSH peaks, ovulation, and subsequent menses.

It is not known whether the cyclic LH-FSH release is a result of inherent central nervous system rhythmicity or caused by some ovarian stimulus related to follicular development. We¹¹⁵ have favored the latter for several reasons: (1) It is difficult to conceive of a slow (month long) central nervous system periodicity. (2) If an inherent central nervous system periodicity existed, one might expect to see aberrantly timed LH peaks occasionally. In fact, in more than 50 studies we have never observed an LH peak to occur outside the midcycle. (3) If an inherent central nervous system cyclicality existed, then study of postmenopausal or castrate women, in whom the elevated FSH-LH concentrations in serum were suppressed to the same concentrations observed in normal women, should reveal periodic LH-FSH peaks. In studies of up to 60 days, we have observed no such

peaks.¹¹⁵ (4) Theoretically it would appear more efficient to link up ovarian follicle development to pituitary secretion assuring a ripe follicle with ovum ready for discharge when the LH peak occurred. Recently, we have demonstrated¹¹⁵ that sequential estrogen and progestogen administered to postmenopausal or castrate women produces an LH-FSH peak exactly resembling the ovulatory peak observed in eugonadal women (Figure 11). It is to be noted in our studies that *estrogen and progestogen* were required to produce the LH-FSH peak. Thus, appropriate alterations in both hormones would appear necessary. It does not appear that progesterone *per se* rises during the menstrual cycle before the LH-FSH ovulatory peak^{116,117} (Figure 12). If preovulatory rises of a progestogen trigger the ovulatory peak, another progestogen must be implicated (for example, 17 hydroxyprogesterone, 20 hydroxy-pregn-4-en-3-one, Δ^5 pregnenolone, pregnenediol, and pregnenetriol).

A number of studies in rabbits and rats lend support to the hypothesis that a progestogen under appropriate circumstances may trigger the ovulatory peak. In 1940-43 Everett showed that ovu-

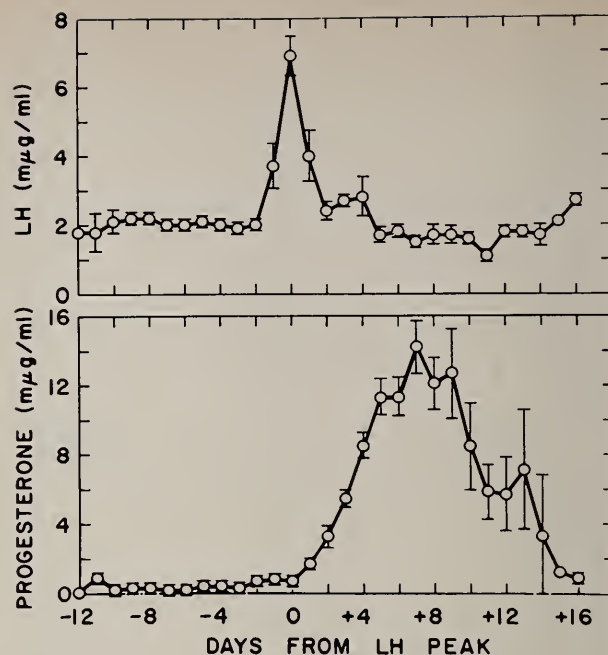


Figure 12.—Composite of four individual menstrual cycles in which LH and progesterone were measured daily. Note the relationship of the LH ovulatory peak to the rise in progesterone. Reproduced with permission from Neill et al.¹¹⁶

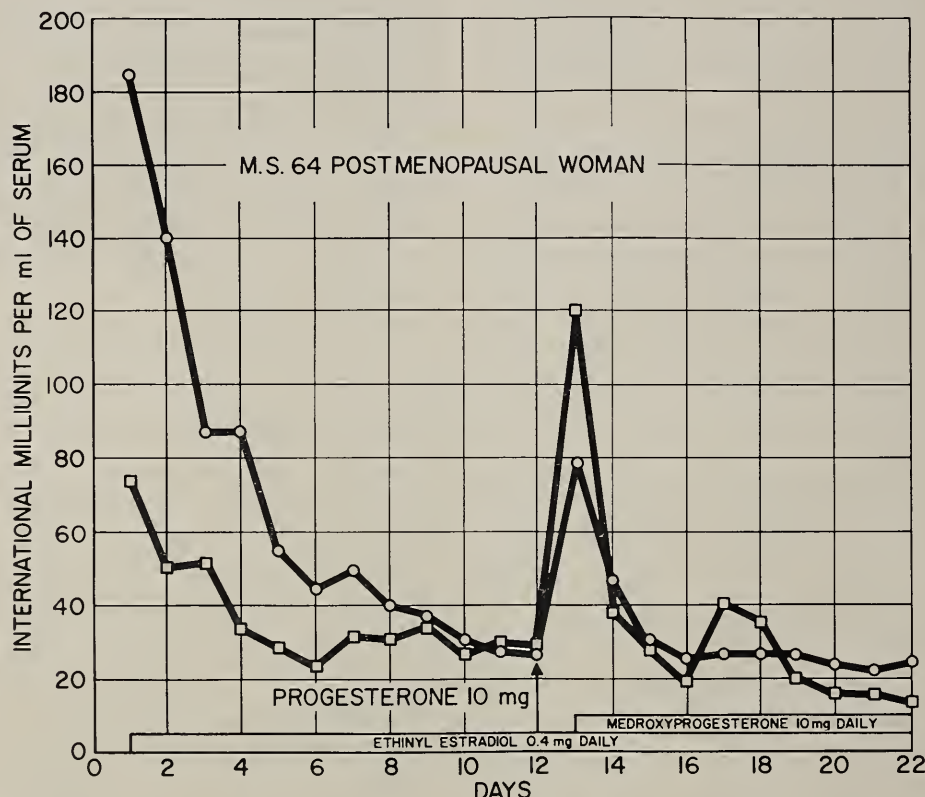


Figure 11.—FSH (O) and LH (\square) concentrations in a postmenopausal woman treated with sequential estrogen plus progestogen. FSH was initially higher than LH and both fell with estrogen treatment. On day 12, 10 mg of progesterone in oil was administered and 24 hours later, LH and FSH had risen, with LH higher than FSH. Medroxyprogesterone was administered orally starting on day 13 and in spite of this continued progesterone, LH and FSH fell and remained low for the remainder of this study. Reproduced with permission from Odell and Swerdloff.¹¹⁵

lation was induced by the administration of progesterone to rats with a spontaneously occurring state of persistent estrus.^{118,119} Greer¹²⁰ subsequently demonstrated that in rats with hypothalamic lesions and resultant persistent estrus, progesterone treatment could produce ovulation. Subsequently, Nallar and coworkers¹²¹ and Redmond and Everett¹²² demonstrated that in normal cycling rats, a single injection of progesterone administered in late diestrus or in proestrus elevated plasma LH. Fraps and Drury¹²³ in 1943 showed that progesterone facilitated ovulation in hens. Pfeiffer¹²⁴ reported that progesterone would induce ovulation during anovulatory summer months in monkeys.

Theoretically it is also conceivable that estrogens (or even other ovarian steroids) might trigger the LH-FSH peak in appropriate circumstances. Supporting evidence of this is scant, however, and further studies are needed. As was stated earlier, low dose estrogen treatment may lead to precocious puberty and, by inference, elevation in LH concentrations.⁸⁷ We have administered high doses of estrogen to eugonadal women and have produced bizarre LH peaks without elevations in FSH.⁹² Studies with low doses of estrogens have not been performed.

Our present premise (and that of many investigators) is that an ovarian signal relates the time of the LH-FSH ovulatory peak to follicular development. (For further discussion, see Odell and Swerdloff.¹¹⁵)

The second level of feedback control existing in females (see Figure 6), analogous to the tonic control of LH and FSH in males, is exemplified by the change in serum LH and FSH concentration which occurs after menopause or castration. Not only do such women lose the cyclic fluctuations referred to above, but basal levels of LH and FSH became elevated (Table 4). This basal elevation of LH and FSH is returned toward normal by estrogen administration (see Figure 13). Animal studies using estrogen implantation or ablation of different areas of the CNS, indicate that this inhibition occurs at the level of the hypothalamus.^{125,126} Furthermore, McCann¹²⁷ demonstrated that injection of hypothalamic median eminence extract resulted in a rapid reappearance of serum LH in estrogen-suppressed rats, indicating that estrogen probably inhibits the secretion of LH releasing factor.

Kuroshima and coworkers¹²⁸ showed that a rapid fall in pituitary FSH occurred in estrogen-

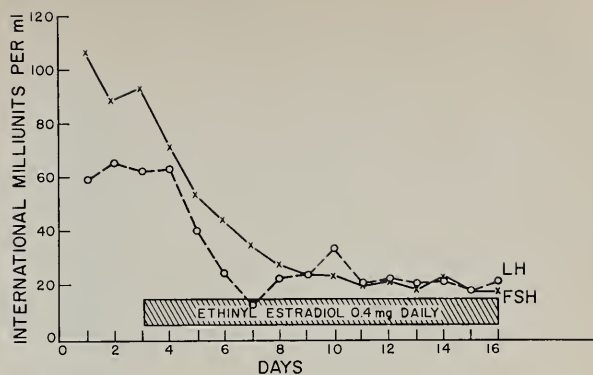


Figure 13.—Decrease in FSH and LH in serum from a 58-year-old castrate woman during three control days and during treatment with 0.4 mg ethinyl estradiol daily. Note the fall over eight days' time. Also note that LH and FSH are both detectable on this dose of estrogen. Reproduced with permission from Odell et al.¹⁰⁵

progesterone suppressed rats (presumably FSH was released from the pituitary). The facilitative role of progesterone as an LH-FSH releaser was discussed. When present chronically, however, progesterone may act with estrogens as a negative feedback inhibitor of LH and FSH. It has been demonstrated that progestogens (including progesterone) plus estrogens inhibit serum LH and FSH concentrations to a greater degree than estrogen alone.¹²⁷ Presumably this is why LH and FSH concentrations are lower during the luteal phase of the menstrual cycle (when both estrogen and progesterone are present) than during the follicular phase (when estrogens alone are present).^{104,105}

Oral Contraceptives and Gonadotropin Secretion

At present there are two main types of generally available contraceptive agents. The first is known as the "non-sequential" pill and contains the combination of an estrogen and progestogen which is given together, usually for 20 to 25 days each month. The second variety is a "sequential" medication in which an estrogen is given alone through the time of expected ovulation, after which progestogen is added to the regimen. Both agents have been shown to inhibit ovulation.¹²⁹⁻¹³²

Figure 14, taken from a study done in our laboratory, demonstrates the effects of both types of contraceptives on serum gonadotropin concentration: the non-sequential drug clearly inhibits both the serum LH and FSH peak. The reader may compare these fluctuations to Figures 9 and 10. The ovulatory peak in eugonadal women consists

SEQUENTIAL CONTRACEPTIVE

NON-SEQUENTIAL CONTRACEPTIVE

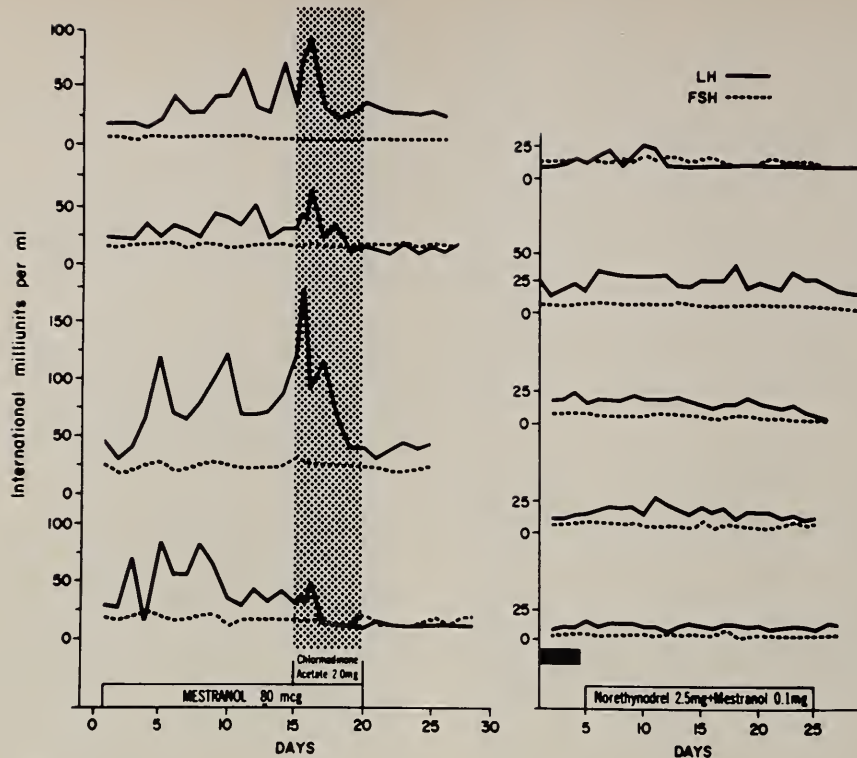


Figure 14.—Daily FSH and LH determinations on serum from four women receiving a sequential estrogen-progestogen contraceptive and from five women receiving a non-sequential estrogen-progestogen contraceptive. The y axis scale is identical for both groups of patients. Note the high LH values with several peaks and low, flat FSH during sequential contraceptive treatment and the low, flat LH and FSH observed during non-sequential contraceptive treatment. Reproduced with permission from Swerdloff and Odell.⁹²

of rises in both LH and FSH. This phenomenon was demonstrated for LH initially by Ross and coworkers,¹³³ and for FSH by Cargille and coworkers.¹⁰⁶ Sequential contraceptives also inhibit the FSH midcycle peak but have a decidedly different effect on LH concentration. One or more LH peaks occurred during the estrogen phase in six of eight subjects, while an additional peak occurred after progestogen in five of the subjects. This demonstrates the potential stimulatory action of estrogen on LH secretion previously referred to.

It is unclear whether the antioviulatory action of the sequential drug is due to the suppression of midcycle FSH peak, the inappropriate LH peaks, or to another cause. One mechanism of action of the *non-sequential* drug can be satisfactorily explained by the flat non-cyclical nature of the daily LH-FSH concentrations.

Pregnancy

In general, pregnancy can be divided endocrinologically into two phases: (1) an initial ovari-

an phase in which the ovary forms the steroids that maintain pregnancy; and, (2) the placental phase when the steroid hormone originates in the foeto-placental unit. The endocrinologic changes that occur in pregnancy represent a complex subject of which a detailed description is beyond the scope of this paper. We will focus on the changes in HCG secretion and refer the readers to several reviews for further details of other endocrine aspects of pregnancy.¹³⁴⁻¹³⁸

The major gonadotropic hormone in human pregnancy urine, human chorionic gonadotropin (HCG), is secreted by the Langhans cells of the chorionic villi of the placenta and acts to stimulate the secretion of progesterone and estrogen by the corpus luteum during the initial phase of pregnancy.¹³⁸ As was stated earlier, HCG has biological and immunological properties clearly resembling those of LH. Certain minor differences exist between the two but the immuno- and bioassays currently available do not distinguish them. This hormone has been shown to be detectable in blood and urine as early as 12 days following ovula-

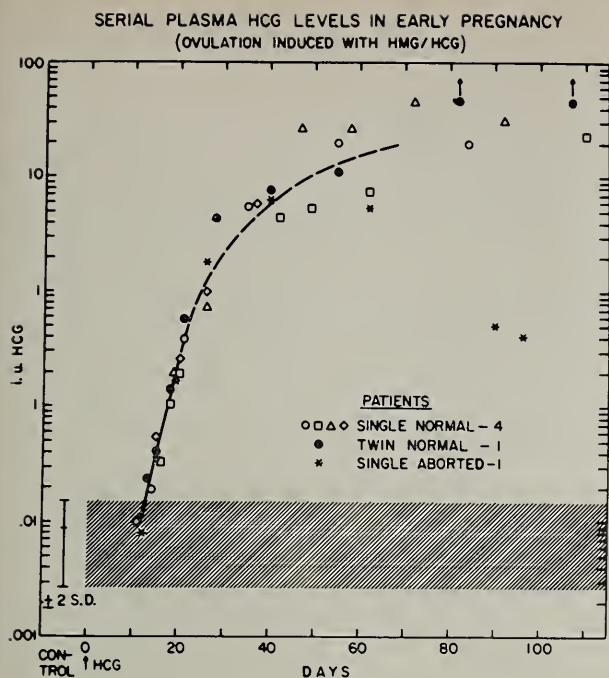


Figure 15.—Daily plasma LH-HCG levels in six women after timed conceptions. The shaded area encompasses normal range of LH-HCG values. Ovulation was induced with HCG after treatment with menopausal gonadotropin and the time of HCG injection is indicated by the arrow. The radioimmunoassay for human LH does not distinguish LH from HCG. Reproduced from Hammond et al with permission.¹³⁹

tion¹³⁹⁻¹⁴¹ and probably two to three days after implantation.

Figure 15¹³⁹ illustrates the plasma concentrations of HCG measured by the radioimmunoassay in six women in whom pregnancy was induced by administration of HCG. Plasma concentrations rise exponentially for about ten days and then begin to plateau. Urinary excretion measured by bioassay reaches peak values (often to 100,000 I.U. per 24 hours) at 45 to 80 days,^{138,142-144} then falls and remains plateaued at above normal levels until after parturition (4,000 to 11,000 I.U. per 24 hours).¹⁴³ Some investigators report a second, lesser rise in the third trimester. Wide⁵⁹ and Hobson and Wide,¹⁴⁵ using a hemagglutination inhibition assay, found higher immunoassay than bioassay values during this same period. Taymor and coworkers, using somewhat different techniques, have not been able to confirm this finding.¹⁴⁶ As chorionic gonadotropin excretion decreases, pregnanediol and estrogen^{138,147-150} rise more rapidly and increase until the end of pregnancy. It is during this transition period that the foeto-placental unit becomes responsible for secretion of the steroid hormones that presumably help maintain pregnancy.¹³⁸ As would be expected

with delivery of the placenta, HCG levels fall.^{144,151} Allison, using an insensitive bioassay method, found that 94 percent of 2,808 women had undetectable HCG levels on the sixth, seventh and eighth days after parturition. In this study, only 1.2 percent of the women had detectable HCG by the tenth day following delivery. Using a hemagglutination inhibition assay, Mishell and coworkers noted that HCG became undetectable by five to six days after delivery.¹⁴⁴

A second placental polypeptide hormone, placental lactogen,¹⁵²⁻¹⁵⁴ is present in retro-placental and maternal blood but not in fetal blood.¹⁵³ It has lactogenic growth hormone-like activity in test animals. While it cross reacts immunologically with HGH, the two substances are not identical. The physiological significance of this substance has not been well defined.

Trophoblastic Tumors

Gonadotropins resembling HCG both immunologically and biologically have been demonstrated to be secreted by such tumors as hydatidiform moles, chorioepitheliomas, choriocarcinoma of the uterus and testis, and by a scattering of other neoplasms.^{1,33,155} Patients with trophoblastic tumors of the uterus have been intensively studied in recent years because of several unusual characteristics of their tumors: (1) The daily excretion of HCG fairly well approximates the amount of viable trophoblastic tissue present in the body. (2) HCG measurement provides a very reliable and accurate means for diagnosing this disease. (3) Choriocarcinoma is very responsive to chemotherapy with a high incidence of complete cures even in patients with widespread metastatic disease. (4) Quantitative measurement of HCG serves as a response index to treatment.¹⁵⁶

For these purposes, it is essential that the assay system used to detect HCG be sensitive enough to detect any concentration above the normal LH level. The mouse uterine weight assay has been used most extensively for treatment and diagnosis,¹⁵⁶ but may be replaced in the future by the radioimmunoassay method. It must be stressed that most commercially available pregnancy tests are not sensitive enough for this purpose.

Prolactin or Luteotropin

No review of the physiology of gonadotropins would be complete without a discussion of prolactin. Because its function in humans remains

completely unknown except for a role in lactation, only a brief discussion is included at the end of this review. This hormone has extremely important functions in lower vertebrates: (1) In amphibians (for example, *Diemyctylus viridescens*) prolactin initiates the second metamorphose and the associated migration to water.¹⁵⁷ (2) In some fish (for example, *Fundulus heteroclitus*) the transition from salt to fresh water is not possible without prolactin¹⁵⁸; cortisol and aldosterone are not effective in allowing this transition. (3) In birds prolactin has an antigonad action; testes of adult pigeons are reduced in weight by 90 percent after ten days of prolactin administration.¹⁵⁹ (4) In rodents, prolactin has been found to be important in reproduction. For example, the females of one strain of dwarfed mice are sterile, but reproduction and lactation can be induced when they are treated with prolactin.¹⁶⁰ In rats and mice prolactin is required for normal function of the corpus luteum.¹⁶¹ Treatment of rats with prolactin furthermore results in prolongation of both the estrous cycle and the life of the corpus luteum. Thus, in rats and mice prolactin is a luteotrophic hormone. To further complicate interpretation of the studies in mice and rats, it has been shown that under some circumstances prolactin may cause luteolysis.¹⁶² In these studies it was pointed out that the morphologic corpus luteum outlived its functional life and prolactin treatment shortened this life.

In cows and sows, hypophysectomy performed soon after ovulation does not influence corpus luteum function; the corpus luteum survives and functions as it would in the intact animal.¹⁶³ Thus, in these species, pituitary hormones including prolactin are not required for corpus luteum function.

In monkeys,¹⁶⁴ and humans¹⁶⁵ prolactin has not been demonstrated to have luteotrophic action. In humans, the function of prolactin is very poorly understood. All that may clearly be said is that prolactin concentrations are elevated in lactating women.¹⁶⁶ No other physiological role of this hormone is known even though it occurs in the blood and pituitary of normal men and women. The latter finding suggests that more sensitive techniques for quantifying prolactin may yet reveal a role of unsuspected importance for this hormone in humans.

REFERENCES

1. Odell, W. D., Hertz, R., Lipsett, M., Ross, G. T., and Hammond, C. B.: Endocrine aspects of trophoblastic neoplasms, Clin. Obstet. Gynec., 10:290-302, 1967.
2. Crowe, S. J., Cushing, H., and Homans, J.: Experimental hypophysectomy, Bull. Johns Hopkins Hosp., 21:127-169, 1910.
3. Evans, H. M., and Long, J. A.: Characteristic effects upon growth, oestrus and ovulation induced by intraperitoneal administration of fresh anterior hypophyseal substance, Anat. Rec., 21:62, 1921.
4. Zondek, B.: Über die funktion des ovariums, Ztschr. f. Geburtsh. U. Gynak., 90:372-380, 1926.
5. Ascheim, S.: Über die funktion des ovariums, Ztschr. f. Geburtsh. U. Gynak., 90:387-392, 1926.
6. Ascheim, S., and Zondek, B.: The hormone of the anterior lobe of the hypophysis and the ovarian hormone in the urine of pregnant women, Klin. Wschr., 6:1322, 1927.
7. Zondek, B.: Über die hormone des hypophysenvorderlappens I. Wachstumshormon, follikelreifungshormon (Prolan A), luteinisierungshormon (Prolan B) stoffweichekshormon, Klin. Wschr., 8:245-248, 1930.
8. Smith, P. E., and Engle, E. T.: Experimental evidence regarding the role of the anterior pituitary in the development and regulation of the genital system, Am. J. Anat., 40:159-217, 1927.
9. Evans, H. M., and Simpson, M. E.: Antagonism of growth and sex hormones of the anterior hypophysis, JAMA, 91:1337-1338, 1928.
10. Weisner, B. P., and Marshall, P. G.: The gonadotropic hormones. I. The preparation and properties of extracts of the anterior lobe, placenta and pregnancy urine, Quart. J. Exp. Physiol., 21:147-179, 1931.
11. Fevold, H. L., Hisaw, F. L., and Leonard, S. L.: The gonad-stimulating and the luteinizing hormones of the anterior lobe of the hypophysis, Am. J. Physiol., 97:291-301, 1931.
12. Moore, C. R., and Price, D.: Gonad hormone functions and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex hormone antagonism, Am. J. Anat., 50:13-72, 1932.
13. Klinefelter, H. F. F., Albright, F., and Griswold, G. C.: Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis, J. Clin. Endocr., 3:529-544, 1943.
14. Harris, G. W., and Jacobson, D.: Functional grafts of the anterior pituitary gland, Proc. Roy. Soc. (Biol.), 139:263-276, 1952.
15. Li, C. H., Simpson, M. E., and Evans, H. M.: Purification of the pituitary interstitial cell stimulating hormone, Science, 92:355-356, 1940.
16. Shedlovsky, T., Rothen, A., Greep, R. O., Van Dyke, H. B., and Chow, B. F.: The isolation in pure form of the interstitial cell stimulating (luteinizing) hormone of the anterior lobe of the pituitary gland, Science, 92:178-180, 1940.
17. Li, C. H.: The chemistry of gonadotropic hormones, Vitamins and Hormones, 7:223-252, 1949.
18. Butt, W. R., Cunningham, F. J., and Hartree, A.: Gonadotropins. Preparation and assay of human pituitary FSH and LH, Proc. Roy. Soc. Med., 57:107-108, 1964.
19. Reichert, L. E., and Parlow, A. F.: Further studies on the purification of human pituitary luteinizing hormone, Endocrinology, 75:815-817, 1964.
20. Reichert, L. E., and Parlow, A. F.: Partial purification and separation of human pituitary gonadotropins, Endocrinology, 74:236-243, 1964.
21. Saxena, B. B., and Ratham, P.: Purification of follicle stimulating hormone from human pituitary gland, J. Biol. Chem., 242:3769-3775, 1967.
22. Odell, W. D., Swain, R. W., and Nydick, M.: Molecular weight of human pituitary gonadotropins as determined by radiation inactivation of biological activity, J. Clin. Endocr., 24:1266-1270, 1964.
23. Reichert, L. E., Kathan, R. H., and Ryan, R. J.: Studies on the composition and properties of immunochemical grade human pituitary follicle stimulating hormone (FSH); comparison with luteinizing hormone (LH), Endocrinology, 82:109-114, 1968.
24. Amir, S. M., and Somers, P. J. as presented in: Butt, W. R., The Chemistry of the Gonadotropins, Charles C Thomas, Springfield, Ill., page 59, 1967.
25. Jirgensons, R.: Optical rotary dispersion of some pituitary hormones, Arch. Biochem. Biophys., 91:123-129, 1960.
26. Li, C. H.: Human pituitary interstitial cell stimulating hormone, In Biology of the Prostate and Related Tissues, Vollmer, E. [ed.] National Cancer Institute Monograph No. 12, U.S. Dept. Health, Education and Welfare, pages 181-187, 1963.
27. Reichert, L. E., and Jiang, N. S.: Comparative gel filtration and density gradient centrifugation studies on heterologous pituitary luteinizing hormones, Endocrinology, 77:78-86, 1965.
28. Kathan, R. H., Reichert, L. E., and Ryan, R. J.: Comparison of carbohydrate and amino acid composition of bovine, ovine and human luteinizing hormone, Endocrinology, 81:45-48, 1967.
29. Got, R., and Bourrillon, R.: Isolement et caractérisation de la gonadotropine chorale humaine, Acta Endocr., Supplement 51, page 1091, 1960.
30. Butt, W. R.: The Chemistry of the Gonadotropins, Charles C Thomas, Springfield, Ill., page 64, 1967.
31. Got, R.: Gonadotropin chorale humaine, Doctoral Thesis, L'Académie de Paris, 1959.
32. Nydick, M., Berry, R. J., and Odell, W. D.: Molecular weight of human chorionic gonadotropin as estimated by means of radiation inactivation of biological activity, J. Clin. Endocr. and Metab., 24:1049-1054, 1964.

33. Odell, W. D.: *In* Textbook of Endocrinology, Williams, R. H. [ed.], W. B. Saunders Co., Philadelphia, Penn., pages 1211-1222, 1968.
34. Cole, H. H., and Hart, G. H.: Potency of blood serum of mares in progressive stages of pregnancy in effecting the sexual maturity of immature rats, *Am. J. Physiol.*, 93:57-68, 1930.
35. Cole, H. H., and Hart, G. H.: Concerning gonadotropic substances in mare serum, *Proc. Soc. Exper. Biol. and Med.*, 32:370-373, 1934.
36. Bangham, D. R., and Grab, B.: The second international standard for chorionic gonadotropin, *Bull. World Health Organization*, 31:111-125, 1965.
37. Reichert, L. E.: Further studies on the purification of human postmenopausal urinary luteinizing hormone, *Endocrinology*, 80:319-323, 1967.
38. Odell, W. D., Reichert, L. E., and Swerdloff, R. S.: Correlation between bioassay and immunoassay of human luteinizing hormone, *In* "Gonadotropins 1968"—Proceedings of the Workshop Conference at Vista Hermosa, Mexico, June 24 to 26, 1968, Rosemberg, E. [ed.], Geron-X, Inc., Los Altos, California (to be published December 1968).
39. Odell, W. D., Reichert, L. E., and Bates, R. W.: Pitfalls in the radioimmunoassay of carbohydrate containing polypeptide hormones, *In* Protein and Polypeptide Hormones, Margoulies, M. [ed.], Excerpta Medica Foundation, Part I, pages 124-128, 1968.
40. Rosemberg, E.: *In* "Gonadotropins 1968"—Proceedings of the Workshop Conference at Vista Hermosa, Mexico, June 24 to 26, 1968, Rosemberg, E. [ed.], Geron-X, Inc., Los Altos, California (to be published December 1968).
41. Hertz, R., Odell, W. D., and Ross, G. T.: Diagnostic implications of primary amenorrhea, *Ann. Int. Med.*, 65:800-820, 1966.
42. Greep, R. O., Van Dyke, H. B., and Chow, B. F.: Use of the anterior lobe of the prostate gland in assay of metakentrin, *Proc. Soc. Exp. Biol.*, 46:644-649, 1941.
43. Karg, H.: Ascorbinsäure dynamik in ovar als gonadotropin-nachweis, *Klin. Wschr.*, 35:643, 1957.
44. Parlow, A. F.: *In* Human Pituitary Gonadotropins, Albert, A. [ed.], Charles C Thomas, Springfield, Ill., page 301, 1961.
45. Sakiz, E., and Guillemin, R.: On the method of ovarian ascorbic acid depletion as a test for luteinizing hormone (LH), *Endocrinology*, 72:804-816, 1963.
46. Pelletier, J.: Etude critique du dosage de ICSH par la methode de l'acide ascorbique ovarien, *Ann. Biol. Anim. Biochem. Biophys.*, 3:307-323, 1963.
47. Bell, E. T., Loraine, J. A., Mukerji, S., and Visultakul, P.: Further observations on the ovarian ascorbic acid depletion test for luteinizing hormone, *J. Endocr.*, 32:1-7, 1965.
48. Keller, P. J.: Some observations on the ascorbic acid depletion assay for luteinizing hormone employing immature female mice, *Endocrinology*, 76:165-168, 1965.
49. Bell, E. T., Mukerji, S., and Loraine, J. A.: A new bioassay method for luteinizing hormone depending on the depletion of rat ovarian cholesterol, *J. Endocr.*, 28:321-328, 1964.
50. Wurtman, R. J.: An effect of luteinizing hormone on the fractional perfusion of the rat ovary, *Endocrinology*, 75:927-933, 1964.
51. Cunningham, F. J.: Induction of ovulation in immature mice as an assay of gonadotropin, *J. Endocr.*, 24:215-221, 1962.
52. Brown, P. S., and Wells, M.: Factors which influence assays of gonadotropin based on the induction of ovulation in mice, *J. Endocr.*, 33:507-514, 1965.
53. Steelman, S. L., and Pohley, F. M.: Assay of the follicle stimulating hormone based on the augmentation with human chorionic gonadotropin, *Endocrinology*, 53:604-616, 1953.
54. Brown, P. S.: The assay of gonadotropin from urine of non-pregnant human subjects, *J. Endocr.*, 13:59-64, 1955.
55. Martin, F. I. R., and Peyton, L.: The specificity of the mouse ovarian augmentation assay for follicle stimulating hormone, *Acta Endocr.*, 56:359-368, 1967.
56. Igarashi, M., and McCann, J. M.: A new sensitive bioassay for follicle stimulating hormone (FSH), *Endocrinology*, 74:440-445, 1964.
57. Ross, I. P., and Brown, P. S.: Specificity in assays of follicle stimulating hormone using mice, *Endocrinology*, 81:1179-1185, 1967.
58. Yalow, R. S., and Berson, S. A.: Immunoassay of endogenous plasma insulin in man, *J. Clin. Invest.*, 39:1157-1175, 1960.
59. Wide, L.: An immunological method for the assay of human chorionic gonadotropin, *Acta Endocr.*, Suppl. 70, pages 11-111, 1962.
60. Paul, W. E., and Odell, W. D.: Radiation inactivation of the immunological and biological activities of human chorionic gonadotropin, *Nature*, 203:979-980, 1964.
61. Odell, W. D., Ross, G. T., and Rayford, P. L.: Radioimmunoassay for human luteinizing hormone, *Metabolism*, 15:287-289, 1966.
62. Midgley, A. R., Jr.: Radioimmunoassay: A method for human chorionic gonadotropin and human luteinizing hormone, *Endocrinology*, 79:10-16, 1966.
63. Franchimont, P.: Dosage radioimmunologique des gonadotropines folliculo stimulante et luteinisante, *J. Lab. Comp.*, 2:303-322, 1966.
64. Odell, W. D., and Parlow, A. F.: Radioimmunoassay for human follicle stimulating hormone, *Clin. Res.*, 15:125, 1962.
65. Midgley, A. R., Jr.: Radioimmunoassay for human follicle stimulating hormone, *J. Clin. Endocr. and Metab.*, 27:295-299, 1967.
66. Faiman, C., and Ryan, R. J.: Radioimmunoassay for human follicle stimulating hormone, *J. Clin. Endocr. and Metab.*, 27:444-447, 1967.
67. Greenwood, F. C.: Immunological proceedings in the assay of protein hormones, *In* Modern Trends in Endocrinology, Gardiner-Hill, H. [ed.], Butterworths, London, pages 288-335, 1967.
68. Everett, J. W.: Central neural control of reproductive functions of the adenohypophysis, *Physiol. Rev.*, 44:373-431, 1964.
69. Guillemin, R., Jutisz, M., and Sakiz, E.: Purification partielle d'un facteur hypothalamique (LRF) stimulant la secretion de l'hormone hypophysaire de luteinisation (LH), *Compt. Rend.*, 256:504-507, 1963.
70. Ramirez, V. D., and McCann, S. M.: Thioglycolate-stable luteinizing hormone and corticotropin releasing factors, *Am. J. Physiol.*, 207:441-445, 1964.
71. Guillemin, R., et al., and Shally, A., et al., *In* The Laurentian Hormone Conference, 1967. To be published in *Rec. Prog. Horm. Res.*, 1968.
72. Barraclough, C. A.: Modification in the CNS regulation of reproduction after the exposure of prepubertal rats to steroid hormones, *Rec. Prog. Horm. Res.*, 22:503-539, 1966.
73. Barraclough, C. A., and Gorski, R. A.: Evidence that the hypothalamus is responsible for androgen-induced sterility in the female, *Endocrinology*, 68:68-79, 1961.
74. Pfeiffer, C. A.: Sexual differences of the hypophyses and their determination by the gonads, *Am. J. Anat.*, 58:195-226, 1936.
75. Barraclough, C. A., and Leatham, J. H.: Infertility induced in mice by single injection of testosterone propionate, *Proc. Soc. Exp. Biol. and Med.*, 85:673-674, 1954.
76. Wilkins, L., Blizzard, R. M., and Migeon, C. J.: Diagnosis and treatment of endocrine disorders in childhood and adolescence, page 51, Charles C Thomas, Springfield, Ill., 1965.
77. Odell, W. D., Ross, G. T., and Rayford, P. L.: Radioimmunoassay for luteinizing hormone in human plasma or serum: physiological studies, *J. Clin. Invest.*, 46:248-255, 1967.
78. Kulin, H. E., Rifkind, A. B., Ross, G. T., and Odell, W. D.: Total gonadotropin activity in the urine of prepubertal children, *J. Clin. Endocr. and Metab.*, 27:1123-1128, 1967.
79. Rifkind, A. B., Kulin, H. E., and Ross, G. T.: Follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the urine of prepubertal children, *J. Clin. Invest.*, 46:1925-1931, 1967.
80. Schalch, D. S., Parlow, A. F., Boon, R. C., and Reichlin, S.: Measurement of human luteinizing hormone in plasma by radioimmunoassay, *J. Clin. Invest.*, 47:665-678, 1968.
81. Saxena, B. B., Demura, H., Gandy, H. M., and Peterson, R. E.: Radioimmunoassay of human follicle stimulating and luteinizing hormones in plasma, *J. Clin. Endocr. and Metab.*, 28:519-534, 1968.
82. Kallas, H.: Puberté precoce par parbiose, *C. R. Soc. Biol.*, 100:979-988, 1929.
83. Byrnes, W. W., and Meyer, R. K.: The inhibition of gonadotropic hormone secretion by physiological doses of estrogen, *Endocrinology*, 48:133-136, 1951.
84. Ramirez, V. D., and McCann, S. M.: Inhibitory effect of testosterone on luteinizing hormone secretion in immature and adult rats, *Endocrinology*, 76:412-417, 1965.
85. Ramirez, V. D., and McCann, S. M.: Comparison of the regulation of luteinizing hormone (LH) secretion in immature and adult rats, *Endocrinology*, 72:452-464, 1963.
86. Hohlweg, W.: Veränderungen des hypophysenvorderlappens und des ovariums nach behandlung mit grossen dosen von follikel hormon, *Klin. Wschr.*, 13:92-95, 1934.
87. Ramirez, V. D., and Sawyer, C. H.: Advancement of puberty in the female rat by estrogen, *Endocrinology*, 76:1158-1168, 1965.
88. Smith, E. R., and Davidson, J. M.: Role of estrogen in the cerebral control of puberty in female rats, *Endocrinology*, 82:100-108, 1968.
89. Morrison, R. L., and Johnson, D. C.: Effects of androgenization in male rats castrated at birth, *J. Endocr.*, 34:117-123, 1966.
90. Pincus, G.: Experimental studies of fertility control by hormonal steroids in mammals, *In* International Congress Series #132, Proc. Second Int. Cong. on Hormonal Steroids, Milan, May 23 to 28, 1966. Martini, L., Fraschini, F., and Motta, M. [eds.], Excerpta Medica, pages 100-110, 1967.
91. De la Lastra, M., and Arrau, J.: Inhibitory action of extracts of human hypothalamus on ovulation in rats, *In* Proceedings of the Eighth International Congress of the International Planned Parenthood Federation, Santiago, Chili, Apr. 9 to 15, 1967. Part IV Basic Science Session, Eckstein, P. [ed.], Stephen Austin and Sons, Hertford, England, pages 453-457, 1967.
92. Swerdloff, R. S., and Odell, W. D.: Some aspects of the control of LH and FSH in humans *In* "Gonadotropins 1968"—Proceedings of the Workshop Conference at Vista Hermosa, Mexico, June 24 to 26, 1968, Rosemberg, E. [ed.], Geron-X, Inc., Los Altos, California (to be published December 1968).
93. Franchimont, P.: Radioimmunoassay of Gonadotropic hormones. *In* Proteins and Polypeptide Hormones, Margoulies, M. [ed.], Part I, Excerpta Medica Foundation, pages 99-116, 1968.
94. Burger, H. G., Brown, J. B., Catt, K. J., Hudson, B., and Stochigt, J. R.: Physiological studies on the secretion of human pituitary luteinizing hormone and gonadal steroids. *In* Proteins and Polypeptide Hormones, Part II, Margoulies, M. [ed.], Excerpta Medica Foundation, pages 412-414, 1968.

95. Faiman, C., and Ryan, R. J.: Diurnal cycle in serum concentrations of follicle stimulating hormone in men, *Nature*, 215:857, 1967.
96. Odell, W. D., and Swerdloff, R. S.: Radioimmunoassay of luteinizing and follicle stimulating hormones in serum. *In* Radioisotopes in Medicine: In Vitro Studies, Hayes, R. L., Goswitz, F. A., and Murphy, B. E. P. [eds.], AEC Symposium Series No. 13 (CONF-671111), Oak Ridge, Tennessee, pages 185-206, 1968.
97. Ramirez, V. D., and McCann, S. M.: Inhibitory effect of testosterone on luteinizing hormone secretion in immature and adult rats, *Endocrinology*, 76:412-417, 1965.
98. Paulsen, C. A.: *In* "Gonadotropins 1968"—Proceedings of the Workshop Conference in Vista Hermosa, Mexico, June 24 to 26, 1968, Rosenberg, E. [ed.], Geron-X, Inc., Los Altos, California (to be published December 1968).
99. McCullagh, D. R., and Schneider, I.: Effect of a non-androgenic testes extract on the estrus cycle in rats, *Endocrinology*, 27:899-902, 1940.
100. Mottram, J. C., and Cramer, W.: On the general effects of exposure to radium on metabolism and tumor growth in the rat and the special effects on testis and pituitary, *Quart. J. Exp. Physiol.*, 13:209, 1923.
101. Johnsen, S. G.: Studies on the testicular hypophyseal feedback mechanism in man, *Acta Endocr.*, Suppl. 90, 45:99-124, 1964.
102. Howard, R. P., Sniffen, R. C., Simmons, F. A., and Albright, F.: Testicular deficiency, a clinical and pathological study, *J. Clin. Endocrinology*, 10:121-186, 1950.
103. Paulsen, C. A.: The Testes; *In* Textbook of Endocrinology, Williams, R. H. [ed.], W. S. Saunders, Philadelphia, page 411, 1968.
104. Ross, G. T., Odell, W. D., and Rayford, P. L.: Luteinizing hormone activity in plasma during the menstrual cycle, *Science*, 155:1679-1680, 1967.
105. Odell, W. D., Parlow, A. F., Cargille, C., and Ross, G. T.: Radioimmunoassay for human follicle stimulating hormone: Physiological studies, *J. Clin. Invest.*, (in press), December 1968.
106. Cargille, C. M., Ross, G. T., Howland, L. A., and Rayford, P. L.: Follicle stimulating and luteinizing hormones (FSH and LH) in plasma during menstrual cycles with and without oral contraceptives, *Clin. Res.*, 16:263, 1968.
107. McArthur, J. W., Worcester, J., and Ingersoll, F. M.: The urinary excretion of interstitial-cell and follicular stimulating hormone activity during the normal menstrual cycle, *J. Clin. Endocr. and Metab.*, 18:1186-1201, 1958.
108. Becker, K. L., and Albert, A.: Urinary excretion of follicle stimulating and luteinizing hormones, *J. Clin. Endocr. and Metab.*, 25:962-974, 1965.
109. Rosenberg, E., and Keller, P. J.: Studies on the urinary excretion of follicle stimulating and luteinizing hormone activity during the menstrual cycle, *J. Endocr. and Metab.*, 25:1262-1274, 1965.
110. Wide, L., and Gemzell, C.: Immunological determination of pituitary luteinizing hormone in the urine of fertile and postmenopausal women and adult men, *Acta Endocr.*, 39:539-546, 1962.
111. Fukushima, M., Stevens, V. C., Gant, C. L., and Vorys, N.: Urinary FSH and LH during the normal menstrual cycle, *J. Clin. Endocr. and Metab.*, 24:205-213, 1964.
112. Stevens, V. C., Vorys, N., Besch, P. K., and Barry, R. D.: The effects of a new oral contraceptive on gonadotropin excretion, *Metabolism*, 14:327-338, 1965.
113. Sato, T., Greenblatt, R. B., and Mahesh, V. B.: Levels of luteinizing hormone during the menstrual cycle determined by immunologic techniques, *Fertility and Sterility*, 16:223-228, 1965.
114. Buckholtz, R.: Studies on the excretion relation of the gonadotropic hormones, FSH and ICSH, in the menstrual cycle, *Zschr. Ges. Exp. Med.*, 128:219-242, 1957.
115. Odell, W. D., and Swerdloff, R. S.: Progesterone induced luteinizing and follicle stimulating hormone surge in postmenopausal women: a simulated ovulatory peak, *Proc. Nat. Acad. Sci.* (in press).
116. Neill, J. D., Johansson, E. D. B., Datta, J. K., and Knobil, E.: Relationship between the plasma levels of luteinizing hormone and progesterone during the normal menstrual cycle, *J. Clin. Endocr. and Metab.*, 27:1167-1173, 1967.
117. Yoshimi, T., and Lipsett, M. B.: The measurement of plasma progesterone, *Steroids*, 11:527-540, 1968.
118. Everett, J. W.: Restoration of ovulatory cycles and corpus luteum formation in persistent-estrous rats by progesterone, *Endocrinology*, 27:681-686, 1940.
119. Everett, J. W.: Further studies on the relationship of progesterone to ovulation and luteinization in the persistent-estrous rat, *Endocrinology*, 32:285-292, 1943.
120. Greer, M. A.: The effect of progesterone on persistent vaginal estrus produced by hypothalamic lesions in the rat, *Endocrinology*, 53:380-390, 1953.
121. Nallar, R. J., Antones-Rodriguez, J., and McCann, S. M.: Effect of progesterone on the level of plasma luteinizing hormone (LH) in normal female rats, *Endocrinology*, 79:907-920, 1966.
122. Redmond, W. C., and Everett, J. W.: LH release facilitated in rats by progesterone injection in early proestrus, Program for the Forty-Ninth Meeting of the Endocrine Society, page 58, 1967.
123. Fraps, R. M., and Drury, A.: Occurrence of premature ovulation in the domestic fowl following administration of progesterone, *Soc. Expt. Biol. & Med.*, 52:346-349, 1943.
124. Pfeiffer, C. A.: Effects of progesterone upon ovulation in the rhesus monkey, *Soc. Expt. Biol. & Med.*, 75:455-458, 1950.
125. Lisk, R. D.: Estrogen-sensitive centers in the hypothalamus of the rat, *J. Expt. Zoology*, 145:197-208, 1960.
126. Hohlweg, W., and Daume, E.: Über die wirkung intrazerebraler verabreichten dienoestrolacetats bei ratten, *Endokrinologie*, 38:46-51, 1959.
127. McCann, S. M.: A hypothalamic luteinizing hormone releasing factor, *Am. J. Physiol.*, 202:395-400, 1962.
128. Kuroshima, A., Arimura, A., Saito, T., Ishida, Y., Bowers, C. Y., and Schally, A. V.: Depletion of pituitary follicle stimulating hormone by beef and pig hypothalamic extracts, *Endocrinology*, 78:1105-1108, 1966.
129. Rudel, H. W., and Martinez, Manautou: *In* Rabinowitz, J. L., and Myerson, R. M.: Topics in Medicinal Chemistry, Interscience Publishers, Division of John Wiley and Son, New York, 1966, page 339.
130. Pincus, G.: Some effects of progesterone and related compounds upon reproduction and early development in mammals, *Acta Endocr. Suppl.* 28:18-36, 1956.
131. Ostergaard, E.: Inhibition of ovulation observed at laparotomy in patients treated with 6-dehydro-6 methyl 17 alpha acetoxy progesterone (DMPA), *International Journal Fertility*, 9:25-28, 1964.
132. Garcia, C. R., Pincus, G., and Rock, J.: Effects of three 19-nor steroids on human ovulation and menstruation, *Am. J. Obst. Gynec.*, 75:82-97, 1958.
133. Ross, G. T., Odell, W. D., and Rayford, P.: Oral contraception and luteinizing hormone, *Lancet*, 2:1255-1256, 1967.
134. Diczfalussy, E.: In vivo biogenesis and metabolism of oestrogens in the foeto-placental unit, *Proc. and International Congress Endoc.*, London, 1964.
135. Lloyd, C. W.: Human reproduction and sexual behavior, Lea & Febiger, Philadelphia, 1964.
136. Lloyd, C. W., and Weisz, J.: Some aspects of reproductive physiology, *Ann. Rev. Physiol.*, 28:267-310, 1966.
137. Ryan, K. J.: Estrogen: blood and placental levels and the factors that control them, *Proc. 2nd International Congr. of Endocr.*, London, pages 727-731, 1964.
138. Lloyd, C. W.: The Ovaries, *In* Textbook of Endocrinology, Williams, R. H. [ed.], Philadelphia, W. B. Saunders, pages 475-479, 1968.
139. Hammond, C. H., Marshall, J., Ross, G. T., and Odell, W. D.: Serum HCG measurements after timed conceptions in women (in preparation).
140. Brown, J. B., Klopfer, A., and Loraine, J. A.: The urinary excretion of oestrogens, pregnanediol and gonadotropins during the menstrual cycle, *J. Endocr.*, 17:401-410, 1958.
141. Jones, G. E. S., Delfo, E., and Stran, H. M.: Chorionic gonadotropin and pregnanediol values in normal pregnancy, *Bull. Johns Hopkins Hosp.*, 72:26, 1944.
142. Loraine, J. A.: Assays of human chorionic gonadotropin in relation to clinical practice, *J. Reprod. Fert.*, 12:23-31, 1966.
143. Loraine, J. A.: Some general principles in the bioassay of anterior pituitary and placental hormones in blood with special reference to clinical problems, CIBA Foundation Colloquia on Endocrinology, Vol. XII, page 19, Churchill, London, 1957.
144. Mishell, D. R., Jr., Wide, L., and Gemzell, C. A.: Immunologic determination of human chorionic gonadotropin in serum, *J. Clin. Endocr.*, 23:125-131, 1963.
145. Hobson, B. M., and Wide, L.: The immunological and biological activity of human chorionic gonadotropin in urine, *Acta Endocr.*, 46:632-638, 1964.
146. Taymor, M. L., Goss, D., and Tamada, T.: Immunologic and biologic titers of human chorionic gonadotropin throughout normal pregnancy, *Fert. & Ster.*, 17:613-620, 1966.
147. Roy, E. J., and MacKay, R. B.: The concentration of oestrogens in blood during pregnancy, *J. B. J. Obstet. and Gynaec.*, Brit. Comm., 69:13-17, 1962.
148. Beling, C. G.: Gel filtration of conjugated urinary oestrogens and its application in clinical assays, *Acta Endocr.*, Suppl. 79, pages 9-98, 1963.
149. Svendsen, R., and Sorensen, B.: The concentration of unconjugated oestrone and 17 B oestradiol in plasma during pregnancy, *Acta Endocr.*, 47:237-244, 1964.
150. Frandsen, V. A.: The excretion of oestriol in normal human pregnancy, *Ejnar Munksgaards Furlag, Copenhagen*, 1963.
151. Allison, R. M.: The evaluation of urinary chorionic gonadotropins in all post-gestational patients in the post Huddersfield area for a period of one year, *J. Obstet. Gynaec. Br. Emp.*, 67:632-640, 1960.
152. Josimovich, J. B., and MacLaren, J. A.: Presence in human placenta and term serum of a highly lactogenic substance immunologically related to pituitary growth hormone, *Endocrinology*, 71:209-220, 1962.
153. Kaplan, S. L., and Grumbach, M. M.: Studies of a human and simian placental hormone with growth hormone-like and prolactin-like activities, *J. Clin. Endocr.*, 24:80-104, 1964.
154. Turkington, R. W., and Topper, Y., Jr.: Stimulation of casein synthesis and histological development of mammary gland for human placental lactogen in vitro, *Endocrinology*, 79:175-181, 1966.
155. Hamburger, C.: Gonadotropins in cases of hydatid mole and chorioepithelioma of the uterus, *In* Wolstenholme, G. E. W., and O'Connor, M. [eds.], CIBA Foundation Colloquia on Endocrinology, Hormone Production in Endocrine Tumors, Little, Brown and Co., Boston, 12:190-193, 1958.

156. Ross, G. T., Hammond, C. B., Lipsett, M. B., and Odell, W. D.: Chemotherapy of metastatic and metastatic gestational trophoblastic neoplasms, *Texas Reports of Biology and Medicine*, 24:326-338, 1966.
157. Nicoll, C. S., Bern, H. A., and Brown, D.: Occurrence of mammatrophic activity (prolactin) in the vertebrate adenohypophysis, *J. Endocr.*, 34:343-354, 1966.
158. Pickford, G. E., and Phillips, J. G.: Prolactin, a factor in promoting survival of hypophysectomized killfish in fresh water, *Science*, 138:454, 1959.
159. Barkke, A.: Reproduction of female dwarf mice treated with prolactin, *J. Reprod. Fert.*, 11:203-206, 1966.
160. Riddle, O., and Bates, R.: Discussed in *Sex and Internal Secretions*, Allen, E., Danforth, C. H., and Daisy, E. A. [eds.], The Williams and Wilkins Co., Baltimore, 1939.

161. Jones, I. C., and Ball, J. N.: Ovarian-pituitary relationships, Chapter 7, *In The Ovary*, Zuckerman, S. [ed.], Academic Press, New York, 1962.
162. Malven, P. V., and Sawyer, C. H.: A luteolytic action of prolactin in hypophysectomized rats, *Endocrinology*, 79:268-274, 1966.
163. Short, R. V.: Ovarian steroid synthesis and secretion in vivo, *Rec. Progr. Horm. Res.*, 20:303-340, 1964.
164. Hisaw, F. L.: The placental gonadotropin and luteal function in monkeys (*Macaca mulatta*), *Yale J. Biol. Med.*, 17:119-137, 1944.
165. Bradbury, J. T., Brown, W. E., and Gray, L. A.: Maintenance of the corpus luteum and physiologic action of progesterone, *Rec. Progr. Horm. Res.*, 5:151-194, 1950.
166. Canfield, C. J., and Bates, R. W.: Nonpuerperal galactorrhea, *New Eng. J. Med.*, 273:897-902, 1965.

HEMATOLOGIC DISORDERS AFTER GASTRECTOMY

"I suppose that you might say there is room for two schools of thought about the management of hematologic disorders in postgastrectomy patients. Since only 50 percent of the patients develop anemia, you might say that any dog is entitled to one bite and wait to see whether your patient develops a deficiency anemia. If you elect to follow this school of thought, I would like to recommend that you don't wait for the outright development of megaloblastosis or iron deficiency, but perhaps survey your patient every six months by doing a serum iron and a serum B₁₂. The decline of serum iron to abnormal levels generally precedes the development of any serious anemia. The decline of vitamin B₁₂ to abnormal levels always precedes the development of megaloblastic marrow, B₁₂ deficiency, and macrocytic anemia.

"The other school of thought would be that the patient should be treated expectantly. How much iron and B₁₂ should be given to prevent the development of deficiency states? We see that the patients do not develop B₁₂ deficiency for at least two years after partial gastrectomy. For this reason, I think that a yearly injection of 1 or 2 mg of B₁₂ would be perfectly adequate as supportive therapy. With regard to iron deficiency, the question isn't one of massive bleeding. The amount of iron that's present in 5 ml of blood is 2 or 3 mg. So these patients are usually just a little bit out of balance, and all they need is supplementation. They don't need therapeutic doses of iron. They need perhaps 10 or 20 or, at most, 30 mg of iron each day. By aiming your therapy at this amount of iron administered with meals, you will avoid any of the symptoms and problems that are usually encountered when you give iron with the standard tablet, which contains 60 mg of elemental iron."

—WILLIAM H. CROSBY, M.D., Boston

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MEDICAL STAFF CONFERENCE

Cardiac Pacing

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* The summary for the patient this morning will be presented by Dr. David G. Johnson.

DR. JOHNSON:† The patient is a 41-year-old Caucasian breadtruck driver. He was a patient in the University of California hospitals for the first time in November 1967, when he was sent from another hospital for further treatment of subacute bacterial endocarditis. As a teenager he was first noted to have a heart murmur, although there had been neither an earlier history of rheumatic fever nor symptoms of such an illness. He remained well, however, participating in football in college and continuing to lead an active life thereafter. His occupation was strenuous and included lifting heavy bread trays. In September of 1967, however, an illness developed characterized by malaise and spiking fevers in the late afternoon. He did not respond to treatment with tetracycline and was admitted to another hospital in September, where three blood cultures grew *Neisseria mucosae* and a diagnosis of bacterial endocarditis was made.

He was treated with penicillin for 28 days. Therapy was stopped when he had an episode characterized by lancinating pain radiating down the back of both legs, pallor and hypotension immediately following the injection of penicillin. Fourteen days after cessation of treatment, fever and malaise again developed. He was readmitted

again to another hospital where a blood culture again grew *Neisseria mucosae*. Treatment with streptomycin and chloromycetin was begun but had little effect on the course of his illness. He was transferred to our hospital 16 November 1967.

On initial physical examination he appeared healthy and well-developed. Blood pressure was 100 mm of mercury systolic and 70 mm diastolic, pulse regular at a rate of 100 and body temperature 38°C. There were no petechiae or splinter hemorrhages or ocular fundal abnormalities. The cervical venous pulse was normal. The carotid arteries had a normal pulse and a transmitted murmur. The chest was clear. The heart was enlarged 2 cm left of the midclavicular line and the apical impulse was somewhat increased. The heart tones were normal and the aortic second sound was absent. There was a loud, harsh grade 4/6 aortic ejection murmur at the base and a grade 2/6 aortic insufficiency murmur. The spleen was palpable two fingerbreadths below the costal margin.

Initial laboratory work showed the following values: hemoglobin 10.8 gm per 100 ml; hematocrit 35 percent; leukocytes 12,600 per cu mm with 86 percent neutrophils and 11 percent lymphocytes; sedimentation rate 90 mm per hour; reticulocytes 0.7 percent; haptoglobin binding power 250 mg per 100 ml (normal 25 to 125); creatinine 1.0 mg per 100 ml; uric acid 3.7 mg per 100 ml; sodium 134 mEq, potassium 4.3 mEq, carbon dioxide 25 mEq and chloride 95 mEq per liter; alkaline phosphatase 15 SJR units (normal

*Lloyd H. Smith, Jr., M.D.: Professor and Chairman, Department of Medicine.

†David G. Johnson, M.D.: Intern in Medicine.

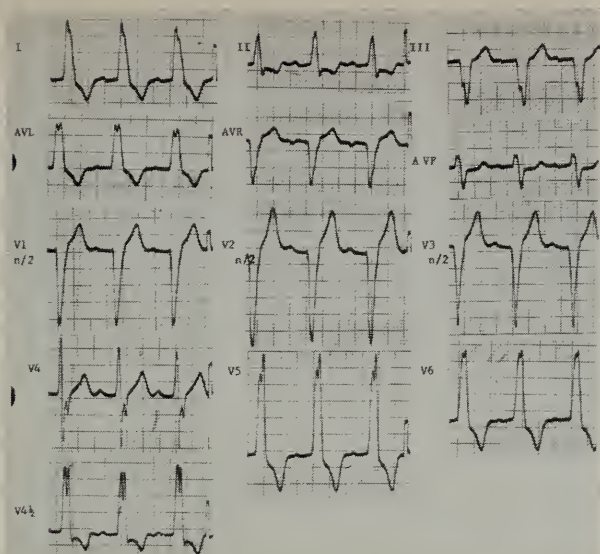


Figure 1.—Cardiogram on admission, showing complete left bundle branch block and first degree A-v block.

2 to 6); bilirubin 1.0 mg per 100 ml total, 0.7 mg per 100 ml conjugated; serum glutamic pyruvic transaminase 21 units; Bromsulphalein® retention 19 percent; prothrombin time 15 seconds (control 13); total protein 7.4 gm per 100 ml with albumin 3.6 gm; alpha-2 globulin slightly elevated to 1.0 and gamma globulin slightly elevated to 1.6 gm per 100 ml. Thyroid function tests showed T_3 uptake normal at 31 percent, butanol extractable iodine normal at 4.7 μ gm per 100 ml.

Penicillin skin tests showed no hypersensitivity reaction. The patient was treated with penicillin, at first 30 million and later 60 million units per day, and streptomycin 1 to 2 gm daily for a course of eight weeks. Fever and erythrocyte sedimentation rate gradually diminished and anemia was corrected. However on 2 December the patient had a syncopal episode which was witnessed by another patient in the same room. An electrocardiogram immediately afterward was not abnormal, but subsequently complete heart block was demonstrated and a second episode occurred.

The patient was taken to the cardiac catheterization laboratory, where a transvenous pacemaker was implanted. He did well for the next three weeks. However, on 24 December he showed signs of ventricular irritability with premature ventricular contractions and bigeminy. The first pacemaker electrode was removed and a second implanted in a position giving less irritability. Subsequently he remained well and began to pace himself. The pacemaker was disconnected after he was monitored for one week in the coronary

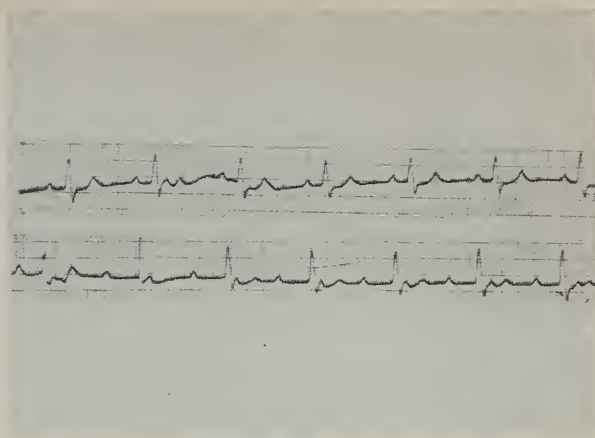


Figure 2.—Cardiogram taken the day after syncopal episode documented complete heart block.

care unit and shown to have continuous sinus rhythm. The patient left the hospital approximately two months after entry. He was afebrile, and had a cardiac rhythm characterized by first degree A-v block and a complete right bundle branch block.

After he had been home only one week he began to have episodes characterized by light headedness followed by flushing and tachycardia. Then in early March 1968 he had a similar episode in which bradycardia, at a rate of 45 per minute, was documented. He was readmitted to our hospital on 5 March for electrocardiographic monitoring. On 7 March a 4-second and a 9-second episode of ventricular asystole were documented, with the patient asymptomatic on both occasions. The following morning he was taken to the operating room and a permanent transvenous pacemaker was implanted. He received a slow infusion of isoproterenol as a precaution. That evening he had hiccups caused by diaphragmatic contractions at the same rate as the pacemaker. It was also noted that the pacemaker was operating continuously although it had been set for demand pacing. When the catheter was seen by x-ray to have slipped from the right ventricle to the right atrium the pacemaker was repositioned. One week later the patient was discharged. Since then he has experienced fatigue, and last evening he complained of having shortness of breath shortly after going to bed.

We have a chronological sequence of cardiograms showing some of his more interesting arrhythmias. The cardiogram at the time of admission (Figure 1) shows a complete left bundle branch block and first degree A-v block. The next one (Figure 2) taken in December on the day

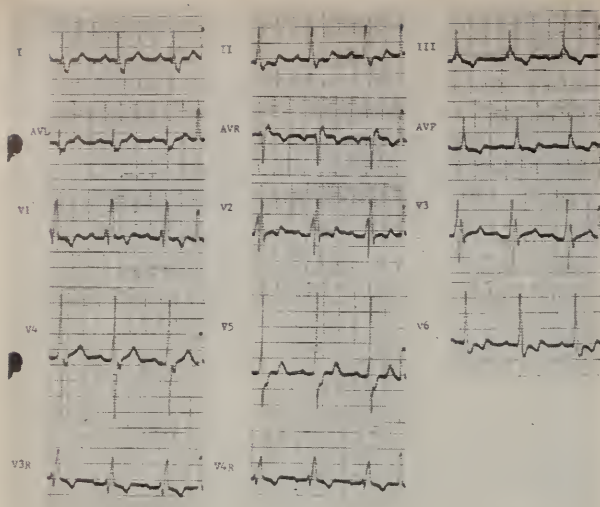


Figure 3.—Cardiogram at time patient left hospital showed first degree A-V block and complete right bundle branch block.

after he had his first syncopal episode documents the complete heart block. The third cardiogram (Figure 3) was taken near the time of discharge in January, and demonstrates first degree A-V block and a complete right bundle branch block. This had been his characteristic rhythm for the month before discharge. Figure 4, a cardiogram taken when the patient was in the coronary care unit during his second admission, demonstrates an episode of ventricular asystole.

This case, an unusual one of bacterial endocarditis complicated by heart block, is presented this morning for the discussion of pacemakers, their uses and complications.

DR. SMITH: Dr. Youker, will you tell us of the x-ray films?

DR. YOUKER:* We have films of the chest obtained in November of 1967. The heart is enlarged with a left ventricular configuration. The ascending aorta is dilated above the aortic valve. The arch is somewhat dilated but nowhere near as dilated as is the ascending portion. A lateral film taken at the same time shows an enlarged heart behind the inferior vena cava. If we follow the shadow of the aorta we see an area of radiopacity which I think represents calcium within the aortic valve. We have an x-ray film taken 9 March 1968 which again shows the same contour, but this time we can see the pacemaker wires in place with a tip in the right ventricle. The battery pack of the pacemaker is shown in the left axilla.

*James Youker, M.D.: Assistant Professor of Radiology.

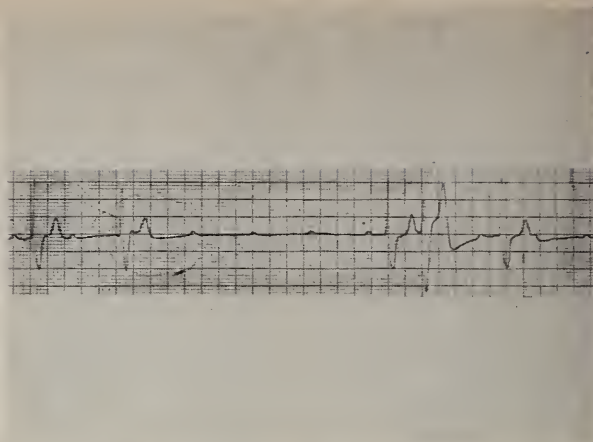


Figure 4.—Cardiogram taken in coronary care unit during patient's second admission demonstrated episode of ventricular asystole.

In summary, we have a patient who shows radiographic changes of aortic valve disease with calcification and a properly positioned pacemaker.

DR. SMITH: The patient has come in for presentation this morning. We have asked Dr. John Hutchinson to present the patient to the audience since Dr. Hutchinson is well acquainted with him.

DR. HUTCHINSON:* This is a group of physicians interested in your case. How are you feeling now?

PATIENT: I have gained a little strength recently.

DR. HUTCHINSON: The patient felt somewhat short of breath this morning and had some elevation of venous pressure, which may be evident to those of you sitting close up. He will probably require some additional salt restriction. (Turning to patient): You have told me that you can tell when this pacemaker fires or does not fire. Can you describe the difference in feeling?

PATIENT: I do get several different sensations. One, that I am getting right now, is a choked up feeling. I perspire at times, and right now I am perspiring. It is functioning. Some other times I feel the wire moving inside there. I have been told that I don't have any sensation there, but I do feel something inside.

DR. HUTCHINSON: The point is that the patient has a demand pacemaker which usually does not fire. It detects sinus rhythm, and firing is then held in abeyance. When the sinus rhythm slows, it fires and he can detect a sensation. We have interpreted this sensation as a combination of the

*John Hutchinson, M.D.: Assistant Clinical Professor of Medicine.

associated bradycardia, for the pacemaker is set at 63, and possibly the absence of the "atrial kick" which is present when he has sinus rhythm. (To the patient): Thank you very much for coming down.

We have presented this interesting man to show several aspects of pacing. I think the cause of his heart disease is probably a congenital bicuspid aortic valve. He has no history of rheumatic fever. Frequently patients like this are found, on surgical operation, to have bicuspid aortic valves which calcify in the mid-thirties and progress to stenosis. With this basic defect, bacterial endocarditis with an unusual organism developed. The patient seems to have been cured of his infection, although we must reserve judgment on that point for some time, of course. In the course of the infection, alternating bundle branch block developed. You may recall that the first cardiogram showed a left bundle branch block and the last cardiogram before pacing showed a right bundle branch pattern. Therefore he had an abnormality of the two bundles which at first occurred at different times and then occurred simultaneously, producing complete heart block.

The clinical problem was whether or not he would require surgical intervention for uncontrollable infection, for rapidly progressive aortic insufficiency, or for complete heart block. There have been several cases in this hospital in which uncontrollable bacterial infection has been controlled by surgical excision of the involved valve with antibiotic coverage. In the present case it was not known whether more rapid progression of the aortic insufficiency would develop due to the infection which might require valve replacement, or whether the heart block was going to be a permanent problem. Either of these situations would have been difficult because it would have involved foreign bodies in the heart in an infected patient. We therefore decided to attempt to tide him over with a temporary pacemaker. Without a pacemaker, unfortunately, he had syncopal spells which were potentially lethal, and a permanent pacemaker seemed indicated. Now it would appear that he is left with significant aortic valve disease and congestive failure. An aortic valve operation may be necessary.

The discussion this morning will be a review of our total experience with pacemakers in this hospital over a ten-year period. I will focus on the permanent units that have been implanted and

TABLE 1.—*Patients Receiving Permanent Pacemakers—August 1959-June 1968*

	<i>Units</i>	<i>Patients</i>	<i>Dead</i>
Endocardial	55	43	7
Epicardial	96	44	16
Total	151	87	23
Total patients treated.....		80	22 (28%)

also consider temporary systems. In the patient presented this morning, the use of both types of devices was demonstrated. I would like to thank Dr. William Vetter for his extensive tabulations from the charts of a large number of patients and to commend the nurses on all the services of the hospitals whose careful tending of the wires and monitors of this large group of patients has helped to avoid any serious misadventures in this ten-year period. More, I would like to reiterate to our surgical colleagues that although pacemaker work frequently seems insignificant, it can result in very gratifying clinical results.

Data on all cases since 1959, when the first pacemaker was implanted, are shown in Table 1. A total of 151 separate units have been placed in 80 patients. Of these the first 96 were epicardial electrodes implanted at thoracotomy and the last 55 new units were endocardial catheters such as those used in today's patient. New patients have come at a rate of about nine a year. During the period, 22 patients died, the time of death ranging from one day to 64 months after pacemaker implantation, with mean survival time 19 months. There are more pacemaker units than patients, the disparity representing the problem of repairs and replacement. It is important to point out that death of only four patients in this group was shown to be related to pacemaker problems. The survivors have had the successful units in place for periods ranging from one week (our most recent case) to 84 months, with the mean survival time 31.6 months and a median of 26 months. There

TABLE 2.—*Causes of A-V Block*

	<i>No. of Cases</i>
Senile heart disease.....	63
Congenital	2
Surgical	10
Other	7
Polymyositis	1
Scleroderma	2
? Rheumatic fever	1
Calcific Aortic Stenosis.....	1
Subacute Bacterial Endocarditis.....	1
Rheumatic Heart Disease.....	1
Total Patients	89

are 12 patients living who have had successful systems in place for 50 or more months.

Table 2 presents the causes of A-V block in this group. The senile heart disease category represents a combination of patients who had either arteriosclerotic changes or had idiopathic heart block of old age, which has been shown to be due to fibrosis of the cardiac skeleton. Most of the patients were of this kind. There were two patients with congenital heart disease, ten patients in whom the block was related to cardiac surgical operations, and seven patients of other types. Both patients with congenital heart disease were in serious trouble with Stokes-Adams attacks at the time of implantation. This situation is unusual since most patients with congenital heart block tolerate it fairly well.

Table 3 shows data on the patients who had surgically-induced heart block. There were four instances of heart block due to aortic valve surgery occurring in 179 aortic valve operations (2.2 percent). There were 255 operations for ventricular septal defect repairs in this same period; in five patients heart block occurred (2.0 percent), and in one patient heart block was associated with a repair of an endocardial cushion defect. These statistics emphasize that in aortic valve operations the risk of causing complete block is fairly high. The node and bundle of His lie very near the outside of the noncoronary cusp. Manipulation of this area with excision of calcium and placement of sutures risks damage to the conduction system. It is valuable to point out that all of the ten patients with heart block resulting from cardiac operations are alive at present by virtue of pacemaking systems.

Of the total group receiving pacemakers approximately two-thirds (54 of 80) had syncopal spells or at least light-headed spells and the other third (26 of 80) had bradycardia and congestive heart failure as the initial manifestation of heart block.

Table 4 summarizes the type of initial rhythms found in the group of 80 patients. Third degree

TABLE 4.—*Initial Rhythm*

3rd degree block	{ Intermittent	20
	{ Fixed	49
2nd degree block	{ Intermittent	9
	{ Fixed	1
Sinus bradycardia		1

heart block occurred in 69, and in about two-thirds of these the block was overcome. In the other third the block was intermittent, as in our patient described this morning. There were ten patients whose highest degree of block was second degree. Most of these had intermittent second degree block, with Stokes-Adams attacks, but some had chronic congestive failure. There was one patient with chronic failure and sinus bradycardia unresponsive to drugs.

Among the indications for permanent pacing, the first, I think, is the demonstration of heart block associated with one well-described or documented fainting spell. This should apply to patients other than those who have had immediate recent myocardial infarction, whose prognosis for subsidence of heart block is good. Patients who have not had recent myocardial infarction, who have a demonstration of heart block, be it permanent or intermittent, who have had one well-documented case of syncope should be strongly considered for implantation of a permanent system.

Number two: All surgical heart block must be treated with a pacemaker system, for the patients do not survive without such systems. This was well learned early in the course of cardiac surgery.

Number three: In the absence of Stokes-Adams attacks, patients who have both bradycardia and circulatory inadequacy which is unresponsive to drug management, can be considered for permanent pacemakers.

As to our initial management of patients before the implantation of a permanent system, eight of the surgically induced heart block patients had electrodes sewn to the heart at the time of cardiac operation when the block was created. These are temporary wires to tide the patient over a period of observation while the surgical injury may heal. Resumption of conduction is seen in about two-thirds of these patients.

In the group with block not induced surgically, there were 30 catheter electrodes placed before the surgical implantation of the pacemaker, and the other 42 patients were satisfactorily managed with drugs alone, usually atropine or isoproterenol. I feel that electrode systems should be used in

TABLE 3.—*Data on Cases of Surgical Heart Block*

Aortic valve	4	(in 179 aortic operations, 1958-1968)
Ventricular septal defect . . .	4	(in 255 ventricular septal defect repairs, 1958-1968)
Tetralogy of Fallot	1	
Endocardial cushion	1	
Total	10	

TABLE 5.—Deaths in a Series of 80 Patients in Whom Cardiac Pacemakers Were Placed

Placement	Deaths	Due to pacer problem	Definitely unrelated	Possibly related
Endocardial	7	2	3	2
Epicardial	15	2	8	5
Total	22	4	11	7

those who seem particularly prone to Stokes-Adams attacks, those who have multiple attacks with a low ventricular escape focus, and those who have had poor response to drug therapy. The physician may start with drug therapy, preferably intravenous isoproterenol; if a patient has a satisfactory acceleration of ventricular rate, then one may be able to manage before and during operation with this drug alone.

An indication for temporary pacing may be a poor and unreliable monitoring system. In such a situation the patient should have the benefit of a temporary pacemaking wire to protect him against the possibility of sudden bradycardia.

The purpose of these wires is, of course, to protect the patient before operation against another attack and to control the rhythm during the induction of anesthesia. Since all anesthesia is, to some degree, a cardiodepressant, there is an increased risk of block and bradycardia at the time of induction.

In addition to prevention of profound bradycardia before and during surgical pacemaker implantation for Stokes-Adams syndrome, a second indication for temporary pacemaking catheter is to define the benefit to be expected from a permanent pacemaker in the patient with heart failure due to bradycardia. He can be evaluated with a temporary pacemaking system to see whether a satisfactory improvement in his circulation is the result of an increased rate alone. One can use the temporary system to determine the optimal pacing rate for improvement of the cardiac output.

Table 5 deals with the causes of death in this group of patients. There were four patients whose death was clearly due to pacer problems, seven in whom the relationship between death and the function of the pacemaker was not clear, and 11 patients in whom death was clearly unrelated to failure of the basic system or to bradycardia. I might say again here that the time of death varied from one day to 64 months after the pacemaker implantation, with a mean of 19 months.

Of the four patients whose death was related to the pacemaker, two had endocardial and two had

TABLE 6.—Complications Other Than Unit Failure

	Placement		Total
	Epicardial	Endocardial	
Infection	11	5	16
Pacing diaphragm	2	1	3
Skin breakdown	2	1	3
Pericardiotomy syndrome	0	2	2

epicardial electrodes. One patient with endocardial electrodes had tricuspid valve endocarditis related to the pacemaker. In the other a purulent infection developed in the pacemaker generator pocket, acute sepsis followed removal of the generator. Both deaths related to epicardial pacemakers occurred early in the course of the pacemaker experience. The patients had external generators and transcutaneous epicardial wires. In one of them chronic staphylococcal pericarditis developed from extension of infection along the wire tracts, then agranulocytosis secondary to chloramphenicol, and finally, fatal staphylococcal septicemia.

Table 6 shows the complications that have occurred other than pacemaker unit failure. Infection leads the list and epicardial electrodes had been used in most of these cases. There were four instances of pacing of the diaphragm, three in which the generator pack was so closely placed to the skin that skin breakdown occurred, and two in which pericardiotomy syndrome developed—interestingly, not in the patients who had pericardiotomy, but rather in those receiving endocardial electrodes, with the pericardium presumably undefiled. Perhaps silent perforation of the ventricular wall had occurred, but this could not be demonstrated, so the cause of pericardial effusion remained undefined.

Table 7 lists the equipment failures. It shows that we use "Medtronic" units most of the time. There have been no wire breaks in the endocardial group and no demonstrated rise in the "threshold" (current required for myocardial stimulation) at the junction between the electrodes and the heart.

Our most difficult problem is the displacement of endocardial electrodes after primary implantation. In the 55 units with endocardial electrode catheter there have been 20 displacements, or 36 percent. The median time of displacement was seven days after the initial operation. As the pacemaker catheter eventually becomes endothelialized against the right atrium and right ventricular wall, displacement rarely occurs late.

The goal of placement is to place the tip of the electrode exactly at the apex of the right ventricle,

TABLE 7.—*Equipment Failure in Various Periods of Follow-up (mean follow-up shown in parentheses)*

<i>Equipment</i>	<i>Placement</i>	<i>Nature of Failure</i>		
		<i>Power Loss No. of Cases</i>	<i>Wire Break</i>	<i>"Exit Block"</i>
Medtronic 117 units	Endocardial	6 16-21 mo. (18.5)	0	0
	Epicardial	13 13-44 mos. (24.4)	9 10-25 mo. (17)	4 6-37 mo. (16)
Electrodyne 17 units		7 14-34 mo. (22)	2 1 & 17 mo. (9)	1 2 mo.
General Electric 15 units		5 9-21 mo. (15)	1 8 mo.	2 1 mo.
Cordis 2 units		1 32 mo.	0	0

from which point it is very difficult for it to move. The wire, which is inserted in the operating room under fluoroscopic visualization, is an elastic rubber-coated spiral which is extremely limp, like wet spaghetti. To stiffen it for implantation, a central stylet is placed, and in my opinion the stylet is a little too soft. It is much more difficult to catheterize the right ventricle precisely with this catheter than with standard cardiac catheters.

We have preferred the endocardial electrode route because it avoids thoracotomy. Many of the patients are elderly and thoracotomy is undesirable. Another reason for preferring these electrodes is that they do not break. Consequently we have used this route exclusively since June 1965. It is reassuring to note that there have been no deaths due to displacement since that time, but the possibility of displacement requires that we monitor the patients immediately after placement of the catheter and for a variable period afterward. Anyone who invents a method for fixing the electrode inside the ventricle will find his suggestions appreciated.

Since June 1967, we have felt that the demand unit is the unit of choice for patients who have intermittent bradycardia, such as the patient presented this morning. We have used demand units also as replacements in patients who resume conduction after they have had a permanent fixed rate pacemaker. So far we have not used demand units for premature ventricular contractions, preferring to try antiarrhythmic drugs, but the deaths among those with late premature ventricular contractions suggests that if drugs are not successful in controlling the aberrant beats, perhaps a demand unit should be considered.

We have used nine demand units since last year, four of them for intermittent A-V block. One of the patients died a week after implantation from a new acute myocardial infarction. We considered there was no relationship between the function of the pacemaker and this death. There were five

units put in as replacements for previous units, when A-V conduction was resumed, and in these cases the patients are doing well. These units have operated now for as long as nine months, but we do not know yet how long they will continue to provide power. Another problem with demand units is deciding whether or not the unit is working. If the patient has resumed sinus rhythm the pacemaker is not firing and the electrocardiogram will show no signal. In that event it is necessary, for test purposes, to slow the patient's sinus rhythm to induce the pacemaker to fire. Methods for doing this include carotid sinus pressure, the Valsalva maneuver, or drug therapy with edrophonium, prostigmin or metaraminol. When the sinus rate slows below the "free-running" rate of the pacemaker, it begins to fire and the impulse can be detected on an electrocardiogram.

Although many of our permanent pacemaker patients have had arteriosclerotic heart disease, in none of them does it appear that complete heart block was due to recent myocardial infarction, and conversely in our coronary care unit we have not had a patient with acute myocardial infarction who both survived and had complete heart block requiring pacemaking. Although we have not put permanent units in any of the patients treated for acute myocardial infarction, we have been vigorous in providing temporary pacemakers for protection of certain patients in the coronary care unit immediately after myocardial infarction. The indications for placing a temporary pacemaking system in acute myocardial infarction include (1) sinus arrest or sinus bradycardia, unresponsive to drug therapy; (2) first degree heart block, particularly if it is a long interval or it is progressive; (3) second or third degree block, either sustained or intermittent; (4) asystole; (5) premature ventricular contractions in some patients or recurrent ventricular tachycardia which cannot be controlled by drugs. Killip expressed belief that any patient with previous cardiac arrest should have a pacer-

maker system and that cardiogenic shock is an indication for a pacemaker catheter. With shock the prognosis is so poor that we tend to do everything that we possibly can to help the patient. In this hospital we have averaged about one such temporary pacing catheter per month for the last two years. So far in none of these cases has a permanent pacer been placed.

With temporary pacemaker systems in the coronary care unit the pacemaker generator is usually of the demand type. We feel that the best method of catheterization is to take the patient to the fluoroscope or the fluoroscope to the patient. There has been a recent wave of interest in "floating" wires, and these may be of use because they do not require the moving of the patient to the fluoroscope. However, they are difficult to place reliably. Only about 80 percent of the time does the catheter float into the ventricle, and even in this successful group considerable time may be required. Hence we prefer fluoroscopic control.

In summary, we have presented a case of complete heart block with unusual etiologic features in which we placed first a temporary pacemaking system, then a demand pacemaker when a competitive rhythm developed, and eventually a permanent pacemaker.

RECENT SUMMARIES FROM THE LITERATURE

1. Bilitch, M., Cosby, R. S., and Cafferky, E. A.: Ventricular fibrillation and competitive pacing, *New Eng. J. Med.*, 276:598, 16 Mar. 1967.
2. Bruce, R. A.: Electrode catheter pacing during acute myocardial infarction, *Amer. Heart J.*, 69:460, 1965.
3. Burchell, H. B., Connolly, D. C., and Ellis, H. F., Jr.: Indications for and results of implanting cardiac pacemakers, *Amer. J. Med.*, 37:764, 1964.
4. Parsonnet, V., Zucker, I. R., Gilbert, L., and Myers, G. H.: Clinical use of an implantable standby pacemaker, *JAMA*, 196:784, 1966.
5. Paulk, A. E., Jr. and Hurst, J. W.: Complete heart block in acute myocardial infarction, *Amer. J. Cardiol.*, 17:695, 1966.
6. Scott, M. E., Geddes, J. S., Patterson, G. C., Adgey, A. A. J., and Pantridge, J. F.: Management of complete heart block complicating acute myocardial infarction, *Lancet*, 2:1382, 30 Dec. 1967.
7. Sowton, E.: Artificial pacing and sinus rhythm, *Brit. Heart J.*, 27:311, 1965.
8. Sowton, E.: Cardiac pacemakers and pacing, *Mod. Conc. Cardiov. Dis.*, 36:31, June 1967.
9. Sowton, E.: Clinical applications of demand pacemakers, *Brit. Med. J.*, 3:576, 2 Sept. 1967.
10. Zucker, I. R.: Competitive idiocardiac and extrinsic pacemaker stimuli in heart block, *Amer. Heart J.*, 69:62, 1965.

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Biological Ethics

The Fantastic Future

G. E. MOORE, M.D., *Buffalo, N.Y.*

WE EASTERNERS ARE well aware of the Western (or should I say Californian) tendency to simplify problems. Naturally the dangers and inherent falseness of some simplifications are evident, and on these occasions I eschew them like the true Easterner that I am not; but for this discussion I propose to use the Californian viewpoint. Simplification is absolutely essential when one attempts to discuss so complex a topic as biological ethics.

In this theoretical essay I will restrict myself to discussing biological ethics in relation to the "improvement" and continued existence of healthy and happy individual humans on this earth. The effect of humans on all levels of plants and animals will be minimized, except as these effects in turn affect humans. No attempt will be made to pay homage to the many important civic and religious mores of our times. The name of the game is not humanity, but the individual human.

About Us

Humans have evolved into amazingly complex organisms with the power to cause radical changes in their environment; this is their most unique characteristic and also the reason that they must assume the greatest burden of responsibility of all creation. Other organisms either adapted to a changing environment by a process of genetic evolution, or perished. But man, in changing his environment to suit his capricious tastes, can develop new "tinker toys" to streak through the air leaving huge trails of waste, or ravage his environment of desirable and perishable plants and animals and minerals,

all with an unbelievable recklessness. His skilled chemists provide ever more powerful compounds which may cause unanticipated havoc in remote areas or to seemingly unrelated organisms. The placid polar bear in his icy fastness is unaware that his fat, too, contains DDT. Compared with his animal neighbors, man has been amazingly destructive, and further he has taken no sustained interest in his effect upon his descendants. To be a completely responsible social animal he should not allow *any* accumulation of artificial waste products, whether they are burned, sunk into subterranean wells, or exhausted into the atmosphere or the surface waters. Gaseous, liquid, and solid wastes provide quantitative evidence of this failure of man's social responsibility. Thus wild tracts and polemics about social and economic problems are to a great extent unnecessary; we can measure our problems by our litter.

Us

Equally acute are the personal problems facing individual physicians and scientists. Reckless use of scientific findings which in themselves are not inherently good or evil, plus the overwhelming desire to know and the possibility of extending life, has created conflict between the scientist's action and the mores of society. The recent advent of heart transplants merely dramatized the fragility of social rules which had already been distorted by the potentials of medical science. Some of this conflict may be temporarily resolved by careful deliberation; the solutions may be valid for a short time — until a new discovery again disrupts social stability.

There is need for a new kind of judiciary and advisory group with omnisocial interests. So far we

The author is Director, Public Health Research, New York State Department of Health.

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Reprint requests to: Director, Public Health Research, New York State Department of Health, 666 Elm Street, Buffalo, N.Y. 14203.

are seeking wisdom about biological ethics by balancing our established mores with the statements of our most heroic and charismatic figure of the moment, be he a young surgeon or an aging philosopher. For example, we are beginning to investigate the ethical problems of transplantation, from the viewpoint of deciding in what part of the body reside the most unique characteristics of an individual — his identity. Most people would not deny that the therapeutic or accidental loss of arms or legs deprives the central nervous system of pleasurable stimuli and robs the body of important neuromuscular functions for survival and maintenance of health in the nervous system. Nevertheless, major amputations—even hemicorporectomy and quadriplegia—do not, from a social standpoint, significantly alter the essence of a patient's personality and identity. Our recognition of this fact is reflected in our strenuous and often commendable efforts to keep such individuals alive.

Transplanted kidneys do not change the identity of the recipients, and it is unlikely that more permanent allogenic transplants of legs, hearts, lungs and other internal organs will cause any more concern of this kind. Indeed, to press the point further, an individual might have all his body parts replaced and still retain the individuality of his genetic packet and his characteristic interaction with the environment—unless the higher centers of his brain were affected. In other words, if Joe receives a new heart, new lungs, new arms, and new legs, to himself and his family he is still Joe, even though he is now a more fragile, allosymbiotic Joe.

Thus the generalization can be made that the unique characteristics of an individual reside in the higher centers. (For convenience only, I will use the term *cerebral cortex*.) Even altering the brain with chemical agents will at some point have to be considered a change in identity. When it becomes possible to preserve and transplant the human brain — an unlikely possibility now but one which will some day have to be faced — new ethical problems will arise. When routine brain transplants are possible, there is little doubt society will conclude that identity is inherent in the brain—not in the fingerprints.

If one accepts the cerebral cortex as the seat of individual identity, the moment of death is easier to define, and one of our knottiest current problems becomes a little easier to handle. One noted author-physician asked whether anyone would bury a per-

son whose heart was still beating. From the point of view of society, the answer must be no; but from the scientist's point of view, the response might just as ethically be yes, *if* the brain were functionless. Cessation of the vital signs is a meaningful criterion of death only in that the static heart and quiet lungs reflect the impending or actual death of the brain. There is no more reason to preserve someone with a viable heart and a dead brain than there is to preserve someone whose heart and brain have long since ceased to function, but whose skin lives on.

The Future Us

These problems are spectacular and immediate; but there are problems of biological ethics more remote, yet of even greater significance for the individual and human society. Problems concerning the moment of death and the identity of a transplantation recipient can be investigated by hearings and legislation, and present decisions can be modified by judicial processes and public opinions.¹

Less tangible problems are equally pressing and more far-reaching in importance, but these cannot be solved by decree or even by public consensus. As an example of one such problem, I refer to our recently developed ability to grow normal human cells in culture. This example will include some scientific jargon and complexities which may tempt the reader to skip to the summary. But read on; it is that temptation to wish for instant understanding which is part of science's social problem.

When human cancer cells were successfully cultured, society did not feel threatened, and little public interest was aroused. There was more interest when a series of investigators began to grow seemingly normal human fibroblasts. Then the question began to arise, "Are human cells really people?"

The question was asked more urgently when the possibility of maintaining an infinite life of normal human cultured cells became a reality.² When normal human cells were first cultured, some scientists concluded that these cultured normal fibroblasts were mortal and could not survive more than 50 or 60 generations. (Generation is used to denote the average time for a culture population to double and thus requires division of the culture into new flasks.) Other scientists disputed Hayflick's claim, but still experience tended to support the thesis of a finite life span of normal cells.

Now in this laboratory we have been successful

in culturing seemingly normal human lymphoblasts from over two hundred individuals; the cell lines have remained in culture for more than two years or over 600 generations without showing any loss of viability or normality. Moreover, we can now assure the infinite life of these cell lines either by continuous culture or by freezing and maintaining them at -196°C , then reculturing the stored cells.

Recognition of the biological and philosophical aspects of this exciting development became evident from the number of people who offered themselves for leukapheresis, and from the interest of these volunteers in whether *their* cells were growing well. One high school student was intensely disappointed when his cell line had to be discontinued because of contamination; and his feelings reflected his deep sense of personal loss. (He was reassured when he found out that we had kept samples of his cells in the cell bank, from which they might be restored at any time.)

Identity of the individuals from whom certain cell lines have been derived is of interest not only to the individual, but also to scientists. In theory, it is desirable to preserve the anonymity of the donor, but emotionally and practically it is much easier to identify cultures by name than by initials or code numbers. Thus RPMI #5287 and RPMI #6237 are commonly referred to as Moore and Flic cells despite attempts to suppress the identities. Even the use of initials or code numbers has not preserved the anonymity of the donors. But one shocking episode proved to us that all cells *should* be coded immediately. A staff member volunteered for leukapheresis and joyfully asked us every few weeks how *her* cells were doing. A permanent cell line was established — with an abnormal karyotype. I decided that this fearful news should be withheld from the childless donor, since on the basis of our present incomplete knowledge we cannot say whether or not the extra minute chromosome is harmful.

In view of the personal nature of these cultured cells, it seems reasonable to obtain an informed consent from the donors unless the cells will be kept for a limited time. For example, a donor might seriously object to his cells being used for venereal disease research, especially if the cells were identified. Most persons, fortunately, consent readily and are pleased by the possibility that their cells may be used in laboratories around the world. Moreover, one can foresee circumstances in which the existence of a cell line might be life-saving to

the donor. For example, if an individual developed a severe lymphopenia, transfusion of his own normal cultured lymphoid cells might constitute useful therapy.

Even if only certain favored cell lines are preserved or continuously cultured, the storage problems will become very troublesome under our present methods. Maintaining 12,000 ampules in liquid nitrogen units and keeping records of them are already a financial burden.

But what of the future implications of growing theoretical people in the laboratory and discarding some in the sink and changing others with drugs and x-ray? Someday, it will be possible to store cells safely for centuries in a satellite orbiting in the intense cold of outer space. (Space vehicles may be unreliable, but they surpass by far the reliability of laboratory freezers.)

Who is to decide whose cells lines will live and whose will be discontinued? It is more than an academic question, since sooner or later it may become possible to grow humans from their cells. The plant physiologists already are able to culture single cells of certain plants and trees until, after several intermediate stages involving changes in culture media, hormones and environmental conditions, a new adult plant develops. One might have dreams or nightmares of someone by-passing decades of research and of circumvention of critical biological principles — to biopsy his favorite movie star or political leader, and grow a dozen of them in the laboratory! Then again, there is some scientific evidence that the genetic packet of a somatic cell could be inserted into an enucleated egg cell to initiate normal differentiation. This intermediate method emphasizes the possible ethical and moral problems of human cell research.

As a concluding jolt, may I state that this recent flurry of interest over the substitution of the nucleus of an intestinal cell into a de-nucleated, fertilized frog egg caused many responses about the legislation of *future* research. But I can think of three ways in which we should be able to produce viable humans from cells right now—so we'd better hurry before the future turns into history, and mankind is shattered in the process.

Legal Problems of "Us Cells"

There are other, more immediate problems associated with the culture of cells from apparently normal individuals. Suppose the cells from a seemingly normal person are found to be abnormal; should

the donor be told that he faces an increased risk of producing abnormal progeny? If the answer is yes, than we may have an obligation to screen all individuals — for their sake if not for society. As noted previously, we have already been faced with such a problem.

The clash between progress in biological research and the stability of human ethics is epitomized by a chromosome anomaly, the XYY syndrome.³ Probably throughout the centuries some odd, tall, perhaps mentally retarded men have committed arson and sexual crimes and exhibited other antisocial behavior. They were treated like other men by the courts until it was found that they had an extra Y chromosome. Thus study of the contents of a single human cell may alter the status of an individual before the court and affect his rights. In some trials involving XYY individuals, verdicts have been altered, and in several notorious cases awaiting trial the Y chromosome may be the chief witness for the defense! The real importance of the XYY syndrome cannot be evaluated until we can determine how many unidentified persons with reasonable social adjustments have the XYY syndrome. Further, other men may have a double dose of the critical genes of second Y chromosome *without* having the extra chromosome. Must they be punished for the lack of a separate packaging of their genes?

The sort of genetic research made possible by the availability of cultured cells may be vitally important to many individuals. For example, it may become possible to correct the expression of genetic defects by several techniques which are now or will be available. The decision as to who will direct this genetic engineering, and in what circumstances it should take place, are problems which must be faced. Even now we can imagine the conflict between good and evil motives that could be wrought by the potential use of these techniques.

The Legislative Problem of Us

The exposition of several aspects of biological research which will sooner or later require specific social, legislative and judicial decisions is not difficult. The problem of assigning responsibility is much more complex. Several important principles are involved; for example, should the judiciary establish new ethical guides? My personal reply is no — their role should be confined to the review of existing legislation. It is evident to any scientist who has tried to provide scientific testimony in court that the rigid rules of examination and cross-

examination and the inability of the jury to keep notes and clarify testimony by direct access to the witnesses may lead to horrendous errors. (I will refrain from commenting on the errors that might be made by aged jurists over-reacting and under-reacting in a vain effort to demonstrate their attunement with the times.) In the case of judgments based upon the presence of an extra Y chromosome, it is likely that equally severe genetic disorders which have no perceptible relationship to civil obedience may not be reflected in a gross change in size or shape of a chromosome — let alone the deletion or addition of an entire structure. Each chromosome probably has from ten to forty thousand genes or more; if individuals are treated uniformly on the basis of the number 46, or the size of the *wrapping* of their gene-bundles, then other individuals with abnormal gene patterns but no recognizable chromosome defects run the risk of injustice in the courts.

A second important principle is the responsibility of the State to clarify a point of biological ethics, once it is raised. In the present example a few scientists interested in genetics or chromosome structure are pursuing their work without, as far as I know, any additional support or urgency except that of the "will to know." Just a few weeks ago we accomplished, to my knowledge for the first time, the establishment of permanent human cell lines from patients with the XXY and XYY syndromes. My colleagues in government expressed scientific curiosity; but otherwise their social interest in this achievement was disheartening. In the circumstances, society should have the right to demand that a special effort be made to clarify the pertinent information so that the legislative and judicial branches of government will act on the basis of the best information available.

The problem is one of timing or of fact. Society must choose to study and regulate theoretical ideas, wait for tangible, new accomplishments, or, as now, delay until someone drops a really big bomb, grubs out a heart or performs some other act which usurps the public's attention.

Now that I have posed several complex problems, I should assume partial responsibility for suggesting solutions. It seems evident that good or bad, or good *and* bad legislative assemblies which are temporarily responsive to their society must have the responsibility for establishing changes in laws affecting biological ethics. It is the responsibility of scientists to keep them informed. The

perennial plea of the legislator for information engenders a feeling of hopelessness when the scientist checks his file of form letters which probably were dictated by a legislator's secretary's assistant. But how then can the facts be gathered, reviewed, and presented in such a way that they will penetrate the people-static which engulfs every legislator? It should not be necessary to produce an "over-kill" event (such as the heart transplants) in order to stimulate action.

Senator Walter F. Mondale (Minnesota) has suggested that a presidential commission undertake studies of the legal, social, and ethical implications of scientific research. An advisory committee to the Congress should be a more effective method of presenting information than holding multiple hearings by congressional committees on subjects of personal, political or categorical importance. Further, hearings which may be attended by only a chairman and one or two sleepy Congressmen are not the epitome of brain-to-brain communication. Contrary to today's fashion, I suggest that the advisory commission not include "consumers" since the consumers will be represented by Congress. Restricting the commission to scientists with interests ranging from animals, vegetables and minerals to the social sciences would aid in limiting its membership to ten or twelve. It would seem

wise to limit appointments by the President to a maximum of six years. (If I dared, I would suggest an age limit of 50 so that it would not become a refuge for retired Deans.)

I am well aware of historical efforts to restrict ideas and thus, in many instances, immortalize them. The commission must consider theory but act on fact. The success of such a group will depend upon the speed with which evaluations of the relative benefits and dangers of drugs, artificial viruses, hybrid cells, psychedelic drugs, radiation sources, and so on, in a broad sense can be accomplished and effective action begun. The commission should not be a substitute for existing surveillance and regulatory units which are needed for everyday problems but for those innovations which may, while converting the future into history, threaten or seriously alter or shatter mankind.

In summary, recent events have provided unchallengeable evidence of a need for a scientific advisory commission to consider the ethical and social aspects of new research findings for us and future mankind.

REFERENCES

1. UCLA Law Review, 15:267 Feb. 1968.
2. Moore, G. E., and McLimans, W. F.: The life span of the cultured normal cell, *J. Theoret. Biol.*, 20:217, Aug. 1968.
3. Casey, M. D., Street, D. R. K., Segall, L. J., McDougall, J. H., McGrath, P. J., and Skinner, J. K.: YY chromosome and antisocial behavior, *Lancet*, 2:859, 15 Oct. 1966.

A WAY TO GET A URINE SPECIMEN FROM A GIRL BABY

"According to a pediatrician I know, the best way to get a urine specimen from a female infant is by capitalizing on one of her natural reflexes — involuntary urination at the time one of her heels is punctured for a blood sample. After cleansing the region of the external urinary meatus, he has one nurse hold the child's legs apart and another hold a container. At the moment the heel is punctured, the infant will usually urinate; and the nurse, holding the labia apart with gloved hands, can collect a clean midstream specimen."

—JOHN C. SHERRIS, M.B., M.D., Seattle

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Is Private Practice Dead?

JOHN S. MILLIS, PH.D., *Cleveland*

THE TOPIC OF my remarks was not necessarily of my choosing. It was assigned to me. I shall not take it literally. The topic in the program is "Is the Private Practice of Medicine Dead?" There are two words in that question which are particularly important. First is the word *private*. It is one of those words that I think we have corrupted and tried to use to express things which it does not mean. The word *private*, from the Latin *privatus*, simply means that it is set apart from the state. It is one of those negative words, for its meaning is not positive, but rather that it is not something else. The best synonym I know for it is voluntary—that is, in contrast to that which is required by law or by dictatorship. It is that which we do from within us. Private is not the antonym of public, for many things are both private and public at the same time. The private practice of medicine is in the public interest and for the public good.

The second word of particular importance in the title is *death*, which is somewhat more difficult to define. I have read a few articles and listened to quite a few discussions about this word recently. One of my good friends in Cleveland, Dr. Claude Beck, maintains that death is not an event but rather a process. I would prefer to use this word in the context that a system or a family or a genus does not die; rather it becomes extinct. Therefore I will modify the title this way: "Will the American Voluntary System of Medical Care Become Extinct?" I have replaced there, you see, the word *private* with the word *voluntary* and the word *dead* with *become extinct*.

My choice of a definition for the word *dead* suggests immediately to you, I am sure, as it did to me, that one might approach this subject

through the analogy, with a consideration of the process of evolution. The basic fact of evolution, as we have all learned, is that those genera with the capacity to adapt to changes in the environment survive. Those without the adaptive capacity die as individuals and become extinct as a genus. Thus, the dinosaur could not adapt but *homo sapiens* could adapt. Perhaps we can approach this question, "Is the voluntary system of medical care about to become extinct?" by analyzing the changing environment and estimating the capacity of the system to adapt to these changes in the environment. I shall not discuss all the factors in the environment which one might think of, but rather choose only six. They are as follows: first, the public's concept of health care; second, the rising expectations of the universal availability of health care; third, the effects of specialization; fourth, the effects of growing institutionalization; fifth, economics; and sixth, and most important in my judgment, the potential of the voluntary way.

The Public Concept of Health Care

Thinking about these factors now one at a time—first, the public concept of health care. It wasn't too long ago that we defined the necessities of life as food, clothing and shelter. Education and health care were not exactly luxuries, but they were things that people, many people, did without because they did not deem them to be as necessary as food, clothing and shelter. But today, our list of necessities has to be amended and I am sure that we would all agree that it would run: food, housing (including sanitation), clothing, education and health care. This is to say, in other words, that health care has shifted from a concept of a privilege to a concept of a right—that is, a necessity. A right is always recognized legally and a right is promised by public policy and by enacted law. It is immediately evident, I think, to all of us that

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The author is Chancellor of Case Western Reserve University.

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Reprint requests to: John S. Millis, Ph.D., Case Western Reserve University, Cleveland, Ohio 44106.

this abrupt change from the role of a privilege to the role of a necessity and a right affects the relationship between supply and demand. Demand escalates by quantum leaps whereas supply must grow only gradually. We therefore have shortages, and shortages always demand accommodations and very difficult choices.

The second change in the environment I would direct your attention to is the rising expectations of our people as to the universal availability of medical care. That this is a changing area and a force of change is a very natural consequence of the change in the concept from that of a privilege to that of a right. But availability is thought of, I think, in four ways. Health care should be available without regard to race, sex, age. Second, it should be available without regard to economic circumstances of those who need it. Third, it should be available without regard to geographical considerations. Fourth, it should be universally available without an adverse effect on the standards of quality. I think we have always accepted the first two of these conditions, namely, the social and economic ones, and certainly medicine's record is a very proud one indeed, for the physician has always cared for the needy. He has given of his time and his energy and of his knowledge without expectations of compensation. I would point out to you that no other profession that I know of, not even the ministry nor teaching, has ever quite acted this way. But we have never considered, I think, the last two conditions as being physically possible. Medical care facilities have always been located to serve the best interests of the greatest number. Inevitably, therefore, they have been more available to some than to others. But we have rationalized this by saying that it was a matter of choice to the individual if he elected to live 50 miles from the nearest physician or 200 miles from the nearest hospital. If he wanted to live in the boondocks, this was his right and his privilege. Our planning of medical care, I think, has usually striven for a balance between quantity and quality, but always recognizing and insisting that there be a minimum of quality and recognizing that, above this minimum, large increments in quality of care must inevitably result in a decrease of the quantity which was available.

Specialization as a Force of Change

The third force of change in the environment which I think is affecting the system of the delivery

of medical care is specialization. Specialization is, of course, inevitable. The increase in knowledge in any field demands a limitation in the area of mastery and, therefore, differentiation among its practitioners. This differentiation must accelerate with time, since knowledge continues to grow, and the greater the knowledge, the smaller the segment one person can possibly manage. The mark of the specialist, as I view him, is that he can perform at a high level of skill in an ever more limited field. Thus medical care, automatically through the force of specialization, becomes of a higher and higher quality and we shall see the same increment in quality in the next two decades that we have seen the last two decades. It is of a higher quality because the skill is more complex and is much more sophisticated. In general, the more sophisticated the skill, the more time is required for its performance and hence there is a decrease in productivity and there is less quantity of service per doctor available. Think only of the time, energy and manpower required for open heart surgery as contrasted to removal of an appendix. A secondary factor is that the organization of the system is such that a specialist works much of his time at a level below his greatest competence, and this is an additional loss of efficiency and of productivity.

My fourth point of change in the environment is the effects of growing institutionalization. There is a generic and inevitable four-step, logical sequence that applies to medicine, industry, education or government equally. First, an increase in knowledge requires differentiation and specialization. Second, specialization results in a division of labor. Third, when there is a division of labor, then organization must inevitably ensue. And fourth, organization demands an institutional framework and therefore the practice of the art or the skill becomes institutionalized. The evidence of this process in medicine is clear. Look at the rise in the importance of the hospital as the center in which we deliver so much of that care. Think about the rise of group practice, another form of institutionalization. Think about the rise of the great clinics, such as the Mayo and the Cleveland clinics, and about the rise, in your own state, of health plans such as the Kaiser Permanente. My point is this, that since knowledge will continue to increase, institutionalization must also increase and the problem in adjusting a one-to-one service of physician to patient in the conditions of an institution is difficult.

The Economics of Quality

The fifth point of change in the environment that I would point to is that of economics. My ideas are relatively simple here. It is obvious to me that productivity is declining with each increment in the quality of care. Second, the efficiency and use of human resources is also declining, or at least it is not increasing. When productivity and efficiency fall, price must rise. It is an inevitable law of economics. But this is not to say, of course, that the higher price did not buy a higher quality. It does say, however, that in a system for the delivery of medical care we have not found the way to get higher quality through increased productivity and higher efficiency. If one would contrast the delivery of medical care to the delivery of, for instance, telephone communications, one would have to say that the Bell System had done much better than the profession of medicine has.

Last, I would ask you to think about the potential of the voluntary way. When I went to school there was a basic assumption concerning the role of government that was very simple. It was government's responsibility to do those things for the citizens which the citizens could not do for themselves. This assumes that much of society's business will be carried out in a voluntary system. But society's problems have become more complex. As we become more urbanized and more industrialized, as the number of people becomes greater, the mechanism to deal with their needs must have greater capacity and higher skills. This is true both in the governmental sector and in voluntary enterprise. Government has recognized this and has tried to organize and to staff itself to cope with increasing complexity and difficulty. In contrast and for the most part, in the voluntary sector, with the exception of industrial corporations, we have tried to make do with the older and unmodified mechanisms. We run universities and hospitals with mechanisms which were developed in the middle of the 19th or even in the 18th century, and wonder why they will not cope with the problems of the last third of the 20th century. This has given rise in the minds of many of our people to the assumption that the voluntary way just simply cannot manage large affairs and be effective in the public interest. But the truth of the matter is that we have never taken the time to look at the voluntary way and decide how, if at all, it can be strengthened and rendered more competent.

Adaptability of the Voluntary System

I come now to the second part of my remarks and some estimates of the capacity of our voluntary system of medical care to adapt to the six factors of change in environment which I have just covered. First, the public concept of health care. Medicine cannot disagree with the concept of the necessity for and, therefore, of the right of people to health care. It has always behaved this way and has done its very best to give care to all. The real problem here is coping with a conflict. A right is legally enforceable and it is enforceable against something or somebody. In our historic concept of medicine, the relationship is directly between patient and physician; and logically, therefore, the right could be enforceable against the physician himself. But this negates the freedom of the physician to accept or reject a patient, which also seems to be a part of the voluntary way. We shall have to look at the possibility of admitting as a matter of public policy that the institutions of medical care are so centrally involved that the right is enforceable against them rather than against the physician as an individual. My judgment here is that organized medicine must examine this question rapidly and probably recognize that the role of the institutions for delivery of care really must be altered to make it capable of response.

My second point of the change in the environment is the expectation as to the universal availability of medical care. We have already accepted this, as I remarked a moment ago, concerning age, sex, color, religion or economic status. But the real problem is to have universal availability without regard to geography and without a decrease in quality. We can mitigate the effects of geography by various programs of collaboration, such as the heart-stroke-cancer legislation. But more importantly, there must be a voluntary end to parochialism and isolation among medical institutions and medical people. We simply have to face up to the fact that not every hospital can be all things, to all patients. We certainly need to do some regional planning and we had better get at it and forget about politics. The problem of quantity versus quality is more difficult. The solution may lie in finding brand new ways to deliver medical care, and I shall speak about that in greater detail in a few minutes.

The third force of change was the effects of specialization. As I mentioned, this is an irreversible trend and where we now see specialization,

next we shall see sub-specialization and 15 years from now there will be sub-sub-specialties. In my judgment a new way to deliver medical care is required. I think there is a growing minimum in the size of the basic organization which will be able to render medical care. We must have a large quantity and high quality simultaneously. We do need a mechanism to produce a greater rationality in the selection of the field of specialization so that we have a more equitable distribution of manpower throughout all fields. We need new forms of differentiation of the physician, new specialties, if you will, such as the primary physician, the creation of which I have been advocating for several years. I would point out to you that these adaptations may prove to be the easiest ones to carry out for they are wholly within the control of organized medicine and you do not have to force government or other parts of our society to agree with you on this.

The fourth point was the growing institutionalization in the delivery of medical care. That's here to stay. It also will grow. The hospital will become more and more central and other kinds of institutions will become more and more the focus for the delivery of medical care. But the only real problem is: How can the physician be involved in the institution and still be free? There is a way. I urge you to look at the university and see if there is an analogy and a parallel there which you can use. In the university we have managed with, I think, good success to serve the necessities of specialization and the division of labor. That is institutionalization, but we have preserved a large degree of freedom for the professional known as teacher. It is done by a process of governance involving large grants of power and responsibility to individuals whom we call officers of instruction or faculty, and by giving other powers to groups of peers which, of course, is the organized faculty.

Research Into Ways to Deliver Health Care

With reference to the question of economics, it seems to me apparent that we cannot cope with the cost problem in the present system of medical care for very long. What, in my judgment, is required, is a second front in medical research. My idea of the second front is research in the delivery of medical care—research with the same kind of attack we have mounted in the bio-medical sciences and which has been so productive and so effective. We must find out how we can use the

knowledge in many other fields, such as, engineering, management, systems engineering, computers, and others. There must be a way to be better and also be more efficient. The findings of the research of the second front, as I call it, will probably be very disruptive of the *status quo* and there will be very many members of the medical profession who won't like it. None of us does like change. But I must remind you that those changes, if voluntarily made, will be far less disruptive than going to a governmental service for the delivery of medical care.

Last, what about the potential non-viability of the voluntary way? This is perhaps the most important point I have to make to you. It precedes all the other adaptations about which I have been speaking and it is fundamental to everything else. The adaptation which we must be able to make voluntarily requires, first, that we realize that change is not a discontinuous phenomenon but a continuous phenomenon. This we learned in evolution, every one of us, years ago. Whenever there is a continuous and continuing evolutionary change, there must be continuing and continuous adaptations. The mechanism which we need, therefore, within organized medicine, is a mechanism designed for evolution, not for revolution and not for the *status quo*, but for one single thing—adaptation. A mechanism to produce and to lead change, and not to oppose it. What I have said is directed to the individuals here. You are the ones that must make the voluntary system work. You are the ones that have committed time and energy and intellectual power to the problems of organized medicine and assumed its responsibilities. You are the ones that must find the way to strengthen your mechanisms so that they are adequate to the task of adaptation of which I have been talking. Though I have used the analogy of evolution, there is one very great difference to which I must call your attention. The adaptive capabilities of the dinosaur were determined in his genes and in his chromosomes. But the adaptive capabilities of organized medicine are determined by intelligence and human will.

How to Succeed with Success

May I close by saying this: I am an eternal optimist and I am an eternal optimist about the medical profession. I do not believe that the voluntary health system of America is about to become extinct. The basis of my belief is that as I look

at medicine and see its problems and listen to you discuss them, wrestle with them, and seek solutions, I am constantly reminded that your problems are problems of success and not problems of failure. If you had not rendered a service which the people of this country had found absolutely essential and necessary, no one would think about it as a right and there would be no demand for universal availability. This is not to say that the problems

are any less severe, less complex, less baffling. It does say something about the spirit with which people like you can adjust themselves to those problems. The same intellectual capacity, the same involvement and dedication, the same creativeness and inventiveness which have brought medicine its huge success and the problems of success, I believe are capable of solving those problems.

STAYING HOME NOT A CURE FOR "SCHOOL PHOBIA"

"Once it's established that a child has a school phobia, the best treatment by far is to get him back in school immediately. The longer the syndrome goes on, the harder it is to treat. While the child is not in school, he does not feel psychiatrically disturbed—that is, whatever conflict he has is resolved by his not going to school. So he's happy as a clam sitting home, and his mother often is a little bit happy as a clam, too, and will act very solicitous toward him. This situation can be terminated by either the parent or the child. The kid can make such a pain in the neck of himself at home if he doesn't want to be there that the mother is forced to send him back to school; or the mother can boot him out of the house and get him back to school.

"The physician can also play a role—particularly early when it's much easier to solve—by absolutely insisting that the child go back to school. In the chronic cases we see, there are often a hundred objections raised: 'If I go back to school, I'll have a stomachache.' 'Well,' I say, 'your stomach aches at home, why couldn't it ache in school?' 'Well, I'll vomit,' he tells me. I say, 'Fine. Take some brown paper bags and vomit in those.' The trick is somehow to create a feeling of inevitability so that whatever happens the child must go to school. Often the school's support must be solicited—that is, the principal, or somebody in the school, must agree to keep the child even if he begins complaining.

"When the child is confronted with a really solid wall, he will very quickly go to school, and there'll be no trouble. This doesn't mean that [going to school] will solve his basic problem, for which the family may need counseling; but I think it's very important to realize that the basic problem is not likely to be solved while the child is at home."

—JEROME L. SCHULMAN, M.D., Chicago

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Computer Science and the Health Care Industry

A Report of the Bureau of Research and Planning, California Medical Association

COMPUTER SCIENCE HAS touched the life of almost every person in the United States. The applications of computer technology, which have become indispensable tools in modern business management, are being investigated and researched by numerous individuals and organizations as they pertain to all facets of the health care industry. The question today is not whether and how the computer is going to assist the physician, but, rather, how will it aid the entire health industry in meeting the demands for more, less costly and improved health services.

Numerous pressures, such as the volume of paper work, the need for more effective reporting, planning, and utilization of time and manpower, have caused physicians, hospital administrators and other health professionals to seek assistance from systems analysts and engineers in tackling a wide variety of problems now confronting the health industry. To determine some of the effect and impact of this new science, a review was made of many articles published in medical and health journals over the past two-year period. The intent of this report is to discuss some of the innovative and exploratory applications of computerization to many elements of health care. The references are briefly cited to provide an overview of the vast amount of material found in the health care publications.

From the perusal of articles on the subject, it appeared that an appropriate grouping of the articles would be according to: Patient Diagnosis and Care, Business Functions, and Planning. These groupings are not separate and distinct entities;

computer technology and scientific application must be considered as components of total systems and their sub-systems.

Patient Diagnosis and Care

The experimentation and research in the application of computer technology to patient diagnosis appears to be more advanced in the areas of mass screening, automated laboratories, patient monitoring, and electrocardiogram interpretation. Electronic data processing in mass screening process is presently being utilized where a large group of patients is tested for a variety of health deviances by means of a battery of tests. Foremost in developing the mass screening technique has been the Kaiser-Permanente Medical Centers in San Francisco and Oakland, California.¹ These two centers process 4,000 cases monthly within a 40-hour weekly schedule. Passing through 20 different stations where tests are performed, a patient completes an extensive series of examinations over a three-hour period. At each station, a specimen is drawn, a test administered or a questionnaire presented. The data on the examinee are then relayed to a computer that has a memory bank which contains information as to the normal limits established for this program. After all tests are recorded, the computer prints out results of each test and indicates whether they are "normal" or "abnormal," based on programmed guidelines in the memory bank. These print-outs are read by an internist. A patient then can be referred for more extensive work-up or treatment, the decision depending upon the physician's evaluation. Some of the tests included in this battery are: electrocardiogram, eight laboratory tests, anthropometry, chest

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and breast x-ray studies and a health perception questionnaire. In Oakland, the results go directly to the computer for analysis, while in the San Francisco facility the punched data cards are read into a data communication system and the data are transmitted via telephone lines to the computer in Oakland, 15 miles away.

A similar multiphasic screening center, modeled after the Kaiser-Permanente program and financed through Regional Medical Programs, is operating, in cooperation with a Neighborhood Health Center, in Tennessee.² Other screening programs financed by Public Health Service are operating in New Orleans, Milwaukee, Providence and Brooklyn.³

One of the most reliable and extensive applications of computer technology has been in automated laboratories. Automated laboratories are being used by more than 150 hospitals in the United States.⁴ From a specimen drawn from a patient, an autoanalyzer machine can perform a series of clinical tests in a very short time. This series of tests can be as extensive as the capabilities and programming instructions given the machine. One article shows how the accumulated results of all the tests done on an autoanalyzer are checked for accuracy by linking the autoanalyzer to the central computer.⁵ Once the accuracy has been confirmed, test results of each patient are printed out on individual patients' reports and dispatched to the nursing station. At Montefiore Hospital in New York, test results are compared, by a computer daily to show whether there has been a cumulated change in the patient over a time span.⁶

Computers have become the mainstay for the vast network of electrocardiogram centers developing in the United States. The largest, by geographical standards, is located at Creighton University School of Medicine in Omaha.⁷ At that center, six specialists work in shifts around the clock interpreting electrocardiograms that are transmitted via the data phone system from rural hospitals and practitioners in Nebraska, Iowa, Missouri, Wyoming and South Dakota. Through computer analysis by telephone circuit, physicians in Hartford Hospital in Connecticut are able to obtain information in eight minutes through a satellite computer from the Public Health Service installation in Washington concerning electrocardiogram readings.⁸

Another vital use of computers is in patient monitoring in acute care units.⁹ In Los Angeles

County Hospital a monitoring system that can measure 24 different physiologic factors simultaneously is linked with a computer that can print out the patient's condition minute by minute. While most hospitals do not have the extensive machinery being used and developed at Los Angeles County Hospital, such bio-electronic research is providing basic data needed by engineers, physicists and physicians to develop a new arsenal of weapons for purposes of disease detection and treatment. In Houston's Methodist Hospital Center, computer technology will allow monitoring of 42 body functions in eight operating rooms simultaneously.⁹ A major stimulus in the development of monitoring systems was the aerospace equipment needed for constant monitor of the astronauts and aquanauts. The great spin-off has been the latent application of equipment in this program to medicine. While much of the equipment and bio-electronic science is not universally accepted and used, many medical schools are beginning to give their students the fundamentals in understanding this science.⁹ Regional Medical Programs will probably be pressed to disseminate information on this entire project.

There are at present over 500 Poison Control Centers operating throughout the United States and its territories. When information is needed, it is generally supplied with the aid of an information system based on card files, books and similar references. Recent advances in computer technology suggest that this technique would increase the efficiency and accuracy in maintaining these centers.¹⁰

Application of computer technology to the taking of medical histories is another field that is being explored by several research groups.¹¹⁻¹⁴ Several methods and tools have been developed to aid research physicians to assess the feasibility of using computers to assist in taking a medical history of a patient. One approach being experimented with by a group^{11,12} is to present to the patient a questionnaire on a cathode-ray screen. The patient's answers are stored on magnetic tape for analysis and print-out. Another group¹⁴ presents to the patient an additional graphic display terminal via a cathode-ray screen. Using pictures of the human body, a patient can point with a pen light to the site of pain. Also, by using the branching technique of the questions, a patient only answers questions relating to his own medical problems; the questioning procedure can be tailored to the

individual patient's age, sex, education or other selected factors.

Although hospitals are not now major users of electronic data processing equipment, a number of developments and pressures are paving the way to more extensive and effective utilization. Some of the most pressing problems that computers might help solve are the need to increase productivity to combat the increasing costs of care, the need for better organized and more efficient departments, and the need to keep up with advancing technology. And a counterpart to these needs is the need for electronic and aerospace industries to develop new markets from knowledge and experience they have gained through the space program. These factors are all related and are forcing the hospital industry to look to some kind of systems-oriented approach to each hospital's internal and external functions. The interest, out of curiosity or necessity, has opened a broad horizon of partnership between many specialists from many industries and disciplines. Words and concepts like "operations research," "systems analysis," and "systems-oriented approach," just to mention a few, are starting to permeate the health field. To some, it is just jargon that sounds good; to others it is something to be avoided; but to the more serious inquirers it is the wave of the future that will enable the health industry to fulfill, in a more effective way, the needs and demands of a health-conscious society.

Accounting, inventory, and similar procedures in hospitals are readily adaptable to electronic data processing. The major factor behind the increasing use of computers for this purpose has been the success business corporations have had in applying accounting functions to machine processing. A previous part of this report cited patient diagnosis as an illustration of adaptability to computer processing. If computers are to assist materially in answering the pressures and demands upon the health care industry, it will be necessary to determine whether the hospital as a communication system can be organized to provide for full integration of this technology. Yoder¹⁵ sees the reorganization and re-thinking of hospital functions to fit the way the computer will function in the future. The literature suggests several approaches which computer technology can take. The first is to buy the "hardware" or equipment and gradually integrate functions from department to department to the machine. Tasks such as dealing with ac-

counts receivable, payroll and inventory are the first to be converted. Another approach is to hire a "software" company that specializes in developing system and sub-system methods and procedures and then recommends equipment of a kind that will fit the particular hospital's needs or task to be performed. Another approach is to adapt a particular company's machinery and methods as a "total package" and apply them to the present organizational structure.

One of the first to adapt the "total package" approach was a hospital in southwest Missouri.¹⁶ Called T.H.I.S. (Total Hospital Information System), the basic elements of this system are: (1) 30,000 pre-punched cards that represent every item in the hospital and every action that might take place; (2) card readers which transmit information from the punched cards to appropriate departments; (3) teletypewriters to translate the punch card data into typewritten orders and reports; and (4) a control computer to amass and store all the information and recall this information as needed and directed. The initial assembling of the punched cards by hand is the responsibility of a unit within the organization. For example, if a physician prescribes an antibiotic to be administered four times a day, the nurse takes the appropriate patient card, medication card, dosage card and time card, and inserts them into the machine. The cards are read by the reader which sends its answers to the pharmacy. This information is also stored in the memory unit of the computer that can calculate the item by quantity and price. The data stay in the memory unit until requested by the accounting department for the individual patient's daily billing. This item, along with other transactions concerning each patient, is accumulated and printed out as directed or programmed.

Many "hardware" and "software" companies are exploring and contracting with individual hospitals for the application of computer technology in hospital activities.¹⁷ Some of the activities being explored are utilization review¹⁸; patient tracing and location¹⁹; patient scheduling by diagnosis, physician's schedule, and room availability²⁰; and clinic patient scheduling,²¹ just to mention a few. Other companies and groups are developing simulation models that can be purchased for adaptation to existing machinery and methods at any hospital.²²

Business Functions

The business functions within hospitals have utilized electronic data processing in one capacity or another for some time. Today there are many service companies in the business of setting up and processing the business aspects of a physician's individual or group practice. Most of these service companies are subsidiaries of large banks or electronic data machinery manufacturers, but some are independent companies specifically established for this purpose. Computers are located at some central location and physicians are hooked into the system either by the phone or by daily mailings. By tying into a shared-time computer system via telephone, a physician, department or institution has an input and output console located at his place of operation. Many consoles can be connected to a single computer and each individual, department or group can communicate and react with the computer system as if it were his exclusively and entirely. Time-sharing systems are being utilized by several hospitals in Wisconsin²³ and by Blue Cross-Blue Shield and hospitals and clinics throughout North Dakota.²⁴ It is through this sharing of computer-time by many physicians in practice that computers have been made adaptable to physicians' office practices. Few physicians could afford to install a computer in their practice, although a large group practice might.²⁵

Another extension of this shared-time concept of computer technology and business practices is the centralized food purchasing and distribution system for the entire state of New York for its mental health institutions.²⁶ Through two major computer centers, the entire food purchasing, distribution, preparation and management is systematically analyzed and programmed to minimize costs. Through such record-keeping procedures, the state has been able to save warehouse space, dispatch shipments directly, buy in quantity, and purchase according to population projections.

Computers are the mainstay of processing most of the medical bills by private insurance organizations and governmental agencies in the United States. One of the more interesting applications of this processing has been put into use by Blue Shield in California, which has developed individual "physician profiles" to assist it in the payment of customary fees and in utilization review of claims.²⁷

Planning

With the passage of much of the recent Federal Government health legislation, the need for socioeconomic data in some compiled form has necessitated the use of computers. Compiled information has assisted California's State Department of Public Health in developing its plans for hospital and related facilities, for community mental health programs, facilities for the mentally retarded, and the Medi-Cal program. The California Health Data Corporation has been established to create a "data bank" of statistical information about patient utilization of hospital facilities statewide.²⁸ A measure of the use of computers in the future is the forecast that by 1972, the health statistics of the entire country of Sweden will be centralized and computerized by individual patient in one location.²⁹

Under Regional Medical Programs established by P.L. 89-239, regional centers will be able to use the computers to disseminate information and instruction.³⁰ The MEDLARS (Medical Literature Analysis and Retrieval System) is designed to store, analyze, and retrieve bibliographic citations to biomedical literature.³¹ From certain centers across the country, individual health personnel have access to over 537,000 citations by medical subject. This compilation is also used to publish *Index Medicus*.

The foregoing examples of the application of computer technology to the professional and business aspects of medical practice and health care represent just a few of the uses to which this new science has been put. While the present focus is primarily on the institutional setting, efforts are being pressed on many fronts relating to the accumulation of demographic data for planning purposes, epidemiological research, programmed instruction and in many areas of activity related to patient care. The experiences gained from the techniques and hardware being developed will inevitably lead to an increasing number of applications to the professional and business aspects of the office practices of physicians, and to linking them to integrated computer systems from which data can be retrieved to fulfill many user requirements. Already as these developments are taking place, several issues and problems associated with the adaptability of this science to the health industry are beginning to appear from various segments. Among these are questions of the confidentiality of records, the compatibility of equipment among

manufacturers and users, and the economic feasibility of using computers.

REFERENCES

1. Collen, Morris F.: Periodic health examinations using automated multitest laboratory, *JAMA*, 195:142-145, Mar. 1966.
2. Elam, Lloyd C.: Health evaluation studies utilizing a multiphasic screen center operating in cooperation with a comprehensive health care program for persons in an urban poverty area, *Proceedings: Conference Workshop on Regional Medical Programs, Public Health Service*, Vol. 2, pp. 1-4, 1968.
3. Anonymous: What are the advantages of mass screen?, *Medical World News*, p. 56, 31 Mar. 1967.
4. *Ibid.*, p. 48.
5. Rappoport, A. E., Gennaro, W. D., and Constandse, W. J.: Cybernetics enters the hospital laboratory, *Mod. Hosp.*, 108:107-111, Apr. 1967.
6. Anonymous: "Casey's Profiles" expand diagnostic role of pathologist, *Mod. Hosp.*, 108:112-113, Apr. 1967.
7. Hermann, J. B., and Carnazzo, A. J.: Dataphone ECG consultation: A model for extension of medical center services to community hospitals, *Proceedings: Conference Workshop on Regional Medical Programs, Public Health Service*, Vol. 2, pp. 117-119, 1968.
8. Anonymous: Computer provides instant ECG diagnosis, *Medical World News*, 100-102, Apr. 1967.
9. Anonymous: Electronics at the bedside, *Medical World News*, pp. 52-59, 5 Aug. 1966.
10. Nadine, J. H., and Rieders, F.: Poison information by digital computer, *Amer. J. Public Health*, 57:1009-1014.
11. Slack, W. V., and Van Cura, L. J.: Computer-based patient interviewing, *Postgrad. Med.*, 43:68-74, Mar. 1968, and 43:115-120, Apr. 1968.
12. Slack, W. V., Peckham, B. M., Van Cura, L. J., and Carr, W. F.: A computer based physical examination system, *JAMA*, 200:224-228, 17 Apr. 1967.
13. Brodman, K., and van Woerkom, A. J.: Computer diagnostic screen for 100 common diseases, *JAMA*, 197:901-905, 12 Sept. 1966.
14. Mayne, J. G., Weksel, W., and Sholtz, P. N.: Toward automating the medical history, *Mayo Clinic Proc.*, 43:1-25, Jan. 1968.
15. Anonymous: Computers open new care patterns, *Blue Cross News*, p. 8, July-Aug. 1968.
16. Anonymous: Missouri hospital receives first installation of new data system, *Mod. Hosp.*, 110:44, Feb. 1968.
17. Anonymous: Medicine: In hot water, *Forbes*, pp. 24-26, 37-38, 15 Mar. 1968.
18. Emrich, R. A., and Zak, E. J.: Computer assists in utilization review, *Hospitals*, 42:56-60, 1 Aug. 1968.
19. Anonymous: Using a data processor to keep constant track of a patient, *Nation's Hospitals*: No. 2, 20-22, 1968.
20. Rosenbaum, C. P.: Record keeping and review in psychiatric clinic, *Hospitals*, 42:70-73, 16 Apr. 1968.
21. Holston, C. A.: Central appointment system for out-patient clinics, *Hospital Management*, 104:65-70, Oct. 1967.
22. Wing, P.: Automated system for scheduling admissions, *Hospital Management*, 104:53-56, Oct. 1967.
23. Anonymous: Hospitals share computer center, *AMA News*, p. 14, 5 Aug. 1968.
24. Hill, C. H., and Laybourn, H.: North Dakota Blue Cross and Blue Shield shared computer programs, *Inquiry*, V:64-69, Sept. 1968.
25. Automation in the medical clinic—A panel discussion, *Group Practice*, 16:177-190, Mar. 1967.
26. Byron, W. E., Flack, K., and Robertson, B.: New York State system embarks on statewide shared service plan, *Mod. Hosp.*, 111:91-97, July 1968.
27. Anonymous: MD self-policing uses Blue Shield data, *Medical World News*, pp. 28-29, 15 Feb. 1968.
28. Anonymous: Statewide hospital data collection system inaugurated, *The Bulletin*, Los Angeles County Medical Association, p. 34, 2 May 1968.
29. Anonymous: Swedish health data to be computerized, *Mod. Hosp.*, 110:24, Jan. 1968.
30. Warner, H., and Budkin, A.: Clinic data collection with a purpose, *Proceedings: Conference Workshop on Regional Medical Programs, Public Health Service*, 2:162-166, 1968.
31. National Library of Medicine: Guide to MEDLARS Service, Department of Health, Education, and Welfare, 1967.

DIAGNOSIS OF OSTEOMALACIA

"The clinical features of osteomalacia are absolutely characteristic: diffuse, wandering, ill-defined, ill-localized pains which the patient may refer to bone, but may equally likely refer to muscle. The radiologist may pick up a Looser's zone, although this is not necessary to the diagnosis. Biochemically, there is nearly always an increase in the serum alkaline phosphatase activity. Histologically, there are osteoid seams which are wider than normal and have many laminae. Finally, the crucial test for the diagnosis is that there should be a response to treatment with vitamin D."

—PROFESSOR PAUL FOURMAN, Leeds, England

Extracted from *Audio-Digest Surgery*, Vol. 15, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

The Scope and Responsibility of Medicine

A Statement Drawn from Contributions to a Forum

This statement was prepared from published and unpublished contributions to a national forum on the scope and responsibility of medicine recently conducted by CALIFORNIA MEDICINE. The editors hope this distillate of the discussions will prove useful to the profession and to the public, and they also wish to express their appreciation to all those in California and elsewhere who have contributed to this forum.

THE SCOPE OF medicine is determined by society. It changes with advances in science, new emphasis in cultural values and growing public sophistication in matters pertaining to health. A fundamental transition in the scope and responsibility is now in progress. Medical science is advancing rapidly, cultural values are changing and there is a new public determination with respect to health and health care. A new definition of health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" is receiving wide acceptance. Health in this definition is becoming the aspiration of millions of Americans. Its attainment for all citizens within the limits of the nation's resources has become an aim of national policy. Society has now determined that medicine will no longer be simply disease-oriented. It is to be health-oriented. It is therefore timely and necessary that both the scope and the responsibility of medicine be reassessed.

SCOPE

The scope of medicine is undergoing substantial change in response to the new concepts of health and a new national commitment for better health care which is to be of high quality and equally accessible to all. The scope of medicine now encompasses the health (1) of individual citizens, (2) of communities of citizens whether rural, urban or regional, (3) of the physical and social environment of human beings, and even (4) the biological health and survival of the human species. The scope of each of these may be briefly indicated as follows:

Personal health care includes the prevention, diagnosis and treatment of individual illness, injury or emotional disturbance; the relief of suffering, restoration of function and rehabilitation of those persons who may have been afflicted; and health maintenance for the individual citizen.

Community health care includes identification of the needs for health care services; development of adequate resources of personnel, equipment and facilities to render these services; and organization locally, regionally or nationally for the delivery of the services for communities of citizens whether rural or urban, advantaged or disadvantaged.

Environmental health care includes concern with both the physical and social environment; with the quality and pollution of air, food and water, and with land resources; with the design and safety of housing, transportation vehicles, streets and highways, population centers and other aspects of the physical environment; and with the health and well-being of the social environment including the family, education, work and recreation, and other social institutions which are part of the human environment.

Genetic and species health care is considered by many already to be within the scope of medicine and to include genetic advice to individuals and families; the application of knowledge to control the quantity of human reproduction and to improve the quality of the human genetic pool; and to improve the health and chances of survival of the human species as such.

RESPONSIBILITY

Medicine cannot assume the entire burden of responsibility for the whole scope of medicine in this new determination, nor is it expected to do so. This responsibility is shared with the other health professions, with the health care industry and indeed with society as a whole. Nor can health care services by themselves ever be expected to achieve the national goals for health, no matter how high their quality or how comprehensive and accessible they may become, because so much that pertains to good health depends upon good nutrition, good housing, sufficient clothing, satisfactory employment and, perhaps most important of all, sufficient education. These are all quite essential to health and must be present not only as preventives of ill health but also as prerequisites to good health care.

Medicine does have a special and unique responsibility which is indeed timeless. This responsibility is to advance its knowledge, skills and ethic and bring these effectively to bear upon the whole scope of medicine as this is determined by society. Throughout its history the subject matter of medicine has always expanded to match the scope, the skills by which this knowledge is put to use have been developed and perfected, and the humanitarian ethic has been applied again and again in the changing circumstances.

Today's new determination of the scope of medicine calls for no change in this basic responsibility. It does call for new knowledge, new skills and new applications of the timeless, humanitarian ethic. It calls for an increase of involvement with other professionals, with the health care industry, and with many other segments of the private and public sectors of society for the betterment of personal health, community health, environmental health and even genetic health.

Personal Health Care

The responsibility for personal health care is shared by the patient, the physician, other health professionals, the health care industry and many other segments of society.

¶ Medicine must find ways for every person to have a personal physician of his own choice who is responsible to him, and who, with his associates, will render personal care for illness or injury, provide leadership and guidance in the use of whatever health care resources may be needed, and give advice with respect to health maintenance and the prevention of illness.

Community Health Care

The responsibility for community health care is shared by medicine, other health professions, the health care industry, consumers and the private and public sectors of society at the local, state and national levels.

¶ Medicine is viewed as the natural leader in community health care and is expected to develop and use the necessary knowledge and skills to fulfill this responsibility.

¶ Medicine is responsible to exercise leadership and expertise to adapt mainstream practice to meet the needs of all, including the poor, the racial minorities and mobile families in both rural and urban America, so that there will be only one level of care equally accessible to all in this nation.

¶ Those responsible for community health care must deal with a substantial disparity between demonstrable needs and relatively scarce resources which projects itself even beyond the foreseeable future.

¶ In collaboration with others who share the responsibility for community health, medicine should seek to identify those services which are truly needed, and try to reduce the demand by eliminating those found not necessary.

¶ In collaboration with others who share the responsibility, medicine should take whatever steps are necessary to expand the numbers, productivity and efficiency of health manpower and scarce health care resources, including facilities such as hospitals, extended care facilities, nursing homes, home care agencies.

¶ In collaboration with others who share the responsibility, medicine should examine new organizational patterns for the delivery of personal health care with respect to their productivity, efficiency and satisfaction to patients, physicians, health care workers and the public.

¶ In collaboration with others who share the responsibility, medicine should develop means of assessing the quality of health care services with respect to scientific and technologic adequacy; availability at the time and place needed; the incentive or motivation to render good service; the effectiveness; the efficiency in terms of producing the desired result with a minimum expenditure or waste of talent, time, money or materials; and satisfaction or fulfillment of reasonable expectations of those who receive, render or otherwise provide for health care.

¶ Medicine is responsible, along with others who share the responsibility, for bringing to bear

upon community health problems not only knowledge, skills and ethic, but also its systems approach of observation, diagnosis, treatment, restoration, prevention and evaluation.

Environmental Health Care

Medicine cannot be responsible for every aspect of environmental health care, since the major responsibility is distributed widely throughout the private and public sectors of society.

¶ Medicine is responsible to bring knowledge, skills and ethic to bear in environmental health care and to work with others in multidisciplinary teams and with community leaders at the local, state and national levels toward better solutions of problems in the physical, economic, social, educational or cultural environment which impinge upon health.

¶ Medicine is responsible to distinguish and identify those social and economic causes of poor health which if remedied by society would reduce the needs for health care and which can never be remedied simply by providing more health care services — that is, poverty, unemployment, poor housing, poor nutrition, inadequate public education, or an unsatisfactory work or recreation environment.

Genetic and Species Health Care

Society has yet to come to grips with the need for applying existing and still-to-come scientific knowledge to the improvement of genetic and species health. Medicine has a responsibility to draw attention to the need for better genetic and species health care.

¶ Medicine is responsible to concern itself with patterns of human reproduction, and to provide leadership, knowledge and expertise to aid in solving problems of population expansion beyond what can be supported in a state of health by the environment.

¶ Medicine is responsible to maintain concern with future scientific progress which may provide means for modification of genes, voluntary sex selection and other advances with potential for profound influence upon species health, and be prepared to develop and apply knowledge, skills and ethic to assist individuals and society with genetic health care.

¶ Medicine is responsible to bring its knowledge, skills and ethic to bear upon matters of human nature and human behavior which enhance or threaten the health and chances of survival of the human species.

¶ Medicine is responsible to develop and use its knowledge, skill and ethic to prevent the degradation of the human genetic pool and even to improve its quality through genetic counseling of individuals and of society.

The Individual Physician's Responsibility

No individual physician can hope to master all the subject matter, learn all the skills or fulfill every responsibility of medicine. This is a corporate task of the medical profession as a whole, working in collaboration with many segments of society. But the individual physician, whether in practice, education, research or whatever, is responsible to do his share to advance the knowledge, skills and ethic of himself and his profession and to bring these to bear to the extent that he is able for the betterment of patient care and the promotion of personal, community, environmental and species health. To fail to do this is to fail a basic professional responsibility in today's society.

¶ The individual physician is responsible not only to maintain and advance his professional competence and skills, but to be of exemplary deportment, moral fiber and personal responsibility.

¶ The individual physician is responsible to apply his knowledge, skills and ethic in the care of the sick and injured, and somehow to strengthen the personal and compassionate aspects of patient care while making full use of the relatively institutionalized and impersonal technology of health care teams, hospitals, laboratories and other organized instrumentalities for delivery of health care services.

¶ The individual physician is responsible to extend his traditional involvement in patient care to active involvement in promoting personal, community, environmental and species health and health care.

¶ The individual physician is responsible to involve himself in health education for patients, communities and the public.

¶ The individual physician is responsible to evaluate himself periodically with respect to his knowledge, skills, productivity, effectiveness, economic efficiency and personal satisfaction and to determine how best to apportion his time and use his talents to fulfill his responsibilities.

Institutional and Organizational Responsibilities

The medical profession as a whole, through all of its instrumentalities, is expected to exercise leadership and provide guidance not only in patient care but in active promotion of improved personal, community,

environmental and species health in their modern definition. Indeed the profession is obligated by its ethic to fulfill this role. This responsibility to lead implies a further responsibility to add new knowledge to the art and science, new skills with which to take the necessary positive actions and improved techniques with which to make public accounting of competence and accomplishment. In fulfilling these responsibilities to lead and to guide, the medical profession, with its exceptionally complex institutional and organizational apparatus, will necessarily collaborate with many other scholarly disciplines, other practicing professions, and many other segments of society. This cumbersome professional machinery may need to be reassessed, improved, and perhaps substantially revised.

Responsibility for Adding New Knowledge

The new scope of medicine as this has been determined by society requires that there be new subject matter in medicine and health science. This new subject matter derives from a broadened conception of health, the principle of equal access for all to health services of high quality, and a new concern with environmental and species health care. The medical profession in all its ramifications is responsible to embrace and advance this new knowledge.

¶ In the modern definition the presence or absence of health is determined by the unique biochemical nature of each human individual and his equally unique life experience in interaction with his physical, emotional and social environment, from the moment of conception until death. These are fundamentally biological phenomena and are subject to immutable biologic law. This new human biology is concerned with the nature and behavior of man and of the human species, and it now becomes a part of medicine and health science.

¶ The national determination that health care services of high quality shall be made equally accessible to all further expands the subject matter of medicine but in a different direction. Supply, demand, distribution, marketing, availability, quality, costs and important moral and ethical questions are all inextricably a part of good patient care. Knowledge and expertise in these areas of health care have now become part of the subject matter of medicine and are appropriate matters for study, research, experiment and professional practice, almost always to be done in collaboration with others.

¶ Similarly, a new familiarity with the subject matter of environmental, genetic and species health must become part of the expertise of medicine.

Responsibility for Action

The timeless ethic of medicine requires that it apply its human compassion and its science toward the goals of good health for all and the betterment of mankind. This is a positive responsibility and demands positive action whether in the treatment of the sick or injured, or in the improvement of personal, community, environmental or species health and health care as these are now defined.

¶ The new human biology, which encompasses the subject matter of traditional medicine and adds new areas of scholarship to health science, must now be developed and applied throughout the entirety of the medical profession including its many educational, research, service and organizational ramifications.

¶ The medical profession must now give a new and high priority to more rapid progress in making an excellent quality of health care equally accessible to all and must consider this equivalent in importance to progress in the technologic treatment of those who are ill or injured.

¶ The medical profession should provide advice, leadership and expertise in finding ways to reduce the disparity between demands for health care and the supply of health services, and to curb costs by improving economic efficiency.

¶ The medical profession should determine what promotes health, by observation, study and research, and with the knowledge thus obtained it should guide the general effort into effective channels. It should participate in and, where necessary, initiate efforts to improve nutrition, housing, education or environmental conditions for better health; and it should use public education, personal persuasion and political pressure where necessary.

¶ The medical profession should participate with other segments of society to find solutions for old and new ethical problems of concern in genetic and species health and health care, for example, fetal health care and abortion, organ transplantation, sexual customs and family life, genetic selection, the morality of euthanasia or of prolonging useless and often unhappy lives sometimes at great social or economic cost.

¶ The medical profession should provide the expertise, advice and guidance to lead communities, states, nations and the world toward better health.

Public Accountability—A New Responsibility

The quality of health care cannot be separated from the cost, and neither of these can be separated from public accountability. The time is long past when the physician was accountable only to his patient for the quality and cost of care. The public in the form of third parties has now become deeply involved in almost every aspect of health care and the accountability of the medical profession for the quality and cost of health care is now a public accountability. Although medicine has a leading role, this responsibility is shared with other health professions, with the health care industry and with various segments of the public and private sectors of society.

¶ The primary responsibility for establishing, maintaining and improving quality in patient care has always rested with the medical profession. This responsibility now extends to a concern with the quality of personal, community, environmental and species health care.

¶ The primary responsibility for establishing, maintaining and improving economic efficiency in health care is at present in limbo. It will fall to whomever in the public or private sector of society becomes recognized as leader in this field. It is incumbent upon the medical profession now to assume this primary responsibility as a necessary extension of its primary responsibility for quality.

¶ The responsibility for leadership in maintaining and improving quality and economic efficiency in health care is now in the nature of a public trust, and carries the further responsibility of public accountability for stewardship of the trust. There must be public evidence of competence and public assessments of productivity, economic efficiency and effectiveness for virtually every facet of health care. There must be public evidence of flexibility and experiment to improve the quality and curtail the cost to society.

¶ Public accountability includes a responsibility to keep the public factually informed concerning problems in health care and progress toward their solution.

CONCLUSION

The scope of medicine is now changed by a wide and increasing acceptance of a broader conception of health and a new determination to make high quality health services equally accessible to every person. New and additional problems are created for medicine. This situation is nothing new to our profession. Throughout its history medicine has added knowledge, skills and new dis-

ciplines. It will now continue to do so, not only to improve traditional patient care, but to fulfill its new responsibilities to promote personal, community, environmental and species health as newly defined by society.

Time presses. Vital decisions often must be made before there is opportunity to develop adequate knowledge or information. This is all too familiar to physicians involved in emergency patient care. It is now occurring in many social and economic aspects of health care. The medical profession has much experience and expertise to contribute in such urgent situations. It is essential that it be on hand, with the best available knowledge, with well developed expertise, informed and skillful representation and responsible leadership to give timely and effective advice and guidance.

Within the structural framework of the profession there is urgent need for more cohesion among the many institutions and organizations of medicine and related groups which have interest in one or another aspect of health. The medical profession must promptly assume a far stronger and more effective central organizational leadership, else society, pressed by the push of events, will perforce and for better or worse assume the leadership through various governmental agencies. Should this occur, what is now called "third party infringement" would in fact become "third party domination."

It is concluded that the scope and the responsibility of medicine are greater than ever before but so are the opportunities to achieve the stated goal of organized medicine in this nation, "The betterment of the public health."

MALCOLM S. M. WATTS, M.D., *Editor*

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Contributors

The views of the following persons on the scope and responsibility of medicine were published in *CALIFORNIA MEDICINE* as part of a national forum, and these views together with some unpublished material form the basis for this statement:

George C. Andersen, M.D., Hermosa Beach
Councilor, Fourth District, California Medical Association
William A. Bellamy, M.D., San Francisco
Associate Clinical Professor of Psychiatry, University of California, San Francisco, School of Medicine; and Past Chairman, Committee on Ethics, American Psychiatric Association

Henrik L. Blum, M.D., Berkeley
Clinical Professor of Community Health Planning, University of California, Berkeley, School of Public Health

John W. Cashman, M.D., M.P.H., Washington, D. C.
*Assistant Surgeon General, U.S. Public Health Service;
and Director, Division of Medical Care Administration,
Public Health Service, and Health Services and Mental
Health Administration, Bureau of Health Services*

Glen G. Cayler, M.D., Sacramento

John B. Dillon, M.D., Los Angeles
*Professor and Chief, Division of Anesthesia, University of
California, Los Angeles, School of Medicine; and
Chairman, Committee on Scientific Assemblies of the
Scientific Board, California Medical Association*

Roger O. Egeberg, M.D., Los Angeles
*Dean, School of Medicine, University of Southern Cali-
fornia*

John R. Gamble, M.D., San Francisco

James W. Haviland, M.D., Seattle
*Member of the American Medical Association Council on
Medical Education*

William D. Holden, M.D., Cleveland
*Professor and Director, Department of Surgery, Case
Western Reserve University School of Medicine, and
University Hospitals of Cleveland*

John H. Knowles, M.D., Boston
General Director, Massachusetts General Hospital

Chauncey D. Leake, Ph.D., San Francisco
*Senior Lecturer in the History of Health Science and
Pharmacology, University of California, San Francisco,
School of Medicine; and Past President, American As-
sociation for the Advancement of Science*

Philip R. Lee, M.D., Washington, D.C.
*Assistant Secretary for Health and Scientific Affairs, U.S.
Department of Health, Education, and Welfare*

Russel V. Lee, M.D., Palo Alto
Consultant, Palo Alto Clinic

Robert S. Long, M.D., Omaha
President, American Society of Internal Medicine

Sherman M. Mellinkoff, M.D., Los Angeles
*Dean, University of California, Los Angeles, School of
Medicine*

Einar O. Mohn, Burlingame
*Chairman, California Council for Health Plan Alterna-
tives; and International Director, Western Conference
of Teamsters*

John G. Morrison, M.D., San Leandro
*Immediate Past President of the California Medical Asso-
ciation*

Jurgen Ruesch, M.D., San Francisco
*Professor of Psychiatry, University of California, San
Francisco, School of Medicine*

Edward B. Shaw, M.D., San Francisco
*Professor Emeritus, Department of Pediatrics, University
of California, San Francisco, School of Medicine; and
Member of the Executive Committee, Scientific Board
of the California Medical Association*

Dwight L. Wilbur, M.D., San Francisco
President, American Medical Association

STERILIZATION OF ANESTHETIC EQUIPMENT

"I think it's high time we as physicians got together with the manufacturers to develop anesthesiology equipment which can be guaranteed safe against contamination. Two physical methods of sterilization should be considered. One is ultra-violet light and the other is ultrasound. High frequency sound above 20,000 cycles will destroy microorganisms. There's a problem of obtaining the organisms in a liquid phase of some kind, but they will nevertheless be destroyed. Second, the use of ultraviolet light should be considered. It might be possible, for instance, to thread your collapsible segment on a light bulb which could be designed for that purpose. Also, the manufacturers could and should consider putting units at various places in the equipment where there is an empty space. I think that this might very appreciably reduce the contamination of the apparatus."

—ROBERT S. HOYT, M.D., Palo Alto

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tion's subscription series of tape-recorded pro-
grams.

Editor
MALCOLM S. M. WATTS, M.D.

•
Associate Editor
LLOYD H. SMITH, JR., M.D.

•
Managing Editor
ROBERT F. EDWARDS
For information on preparation of
manuscript, see advertising page 2

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San Francisco

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San Francisco

**California
Medicine**

EDITORIAL

A Call to Action

THIS ISSUE OF CALIFORNIA MEDICINE offers its readers some quite unusual fare. The Fourth Progress Report of the Committee on the Role of Medicine in Society (May 1968, pages 388 to 395) pointed to the need for a clearer consensus with respect to the scope and responsibility of medicine in the environment of today's changing attitudes toward health and health care. Four reports in this issue are of particular interest in this connection.

1. A distinguished scholar and friendly critic of medicine considers the question "Is Private Practice Dead?" or "Will the American Voluntary System of Medical Care Become Extinct?"

2. A group of thoughtful and responsible student leaders at a California medical school present their views on medical education and social responsibility in an unexpected and warmly welcomed "Letter to the Editor."

3. An imaginative and perspicacious director of research in the Department of Public Health of another state examines some of what is going on in basic biological research and calls for a Presidential commission to undertake studies of the legal, social and ethical implications of what is occurring in scientific research.

4. Lastly there appears the editors' promised distillate of published and unpublished contribu-

tions to a forum on the "Scope and Responsibility of Medicine" which has been conducted by this journal for half a year, and which drew upon the views of many distinguished leaders from California and across the nation as well as a number of toilers in the vineyards here and there.

While there are a number of threads and themes which run through these reports, and one can even begin to see some of the threads weaving themselves into ill-defined patterns and some of the themes falling into some sort of yet vague conceptual frameworks, there is also a message in all these reports which comes through loud and clear. It is a call to action. It is a plea, almost a prayer, or in terms of a current cultural colloquialism a demand that the private non-governmental approach assert itself and that the voluntary system of American medicine rise to meet the challenges inherent in the health care problems of today and also of tomorrow. It is a call upon American medicine to exercise imaginative leadership, cooperative effort, and through realistic and constructive action to prove once again the validity of that uniquely American article of faith, that our free voluntary system can do what needs to be done better, more quickly, more efficiently and with higher quality than any bureaucratic governmental organization or system.

It is now abundantly clear that this article of faith which has made America the great nation it has become is once again to be tested. Once again it must be proved that it is still valid and that it still works. We in organized medicine have always given it lip service, have often extolled it, but generally have left to others the proof of validity. Now it is our turn. The question before us is, can or will this principle be made to work in health

care? Can or will it be made to find the answers which must be found, and can or will it make them work to the satisfaction of the profession and the public? This is an unprecedented opportunity to apply the American voluntary cooperative approach to the whole scope and responsibility of medicine as this is now defined. Can or will the leaders of organized medicine, as the natural leaders within the voluntary system of health care, recognize a responsibility to address themselves to these problems and find the way? Can or will the individuals and the corpus of medicine recognize and accept a responsibility to make a free yet necessarily cooperative, coordinated though ever changing system of health care really work? It would seem that there is needed not only a theoretical consensus with respect to what is the scope and responsibility of medicine, but also a very practical consensus that medicine through its professional organizations will undertake whatever is necessary to prove that whatever needs to be done in health care can be done more efficiently and better within a voluntary system of innovation, cooperation and coordination.

Let us in organized medicine step forward and respond to this call to action. It is our turn to prove that the voluntary American way can do what needs to be done and do it better. Let there not only be consensus but let there be positive action for all to see.

Elections and Illusions

THE RECENT ELECTION gave added emphasis to what should have been obvious for a long time. The voters at an election can make a clear choice and elect one of a limited number of candidates to a public office or give a yes or no answer to any proposition as it is stated, and this is about all that they can do at the ballot box. The belief that just because they choose a candidate over his opponents means that the voters endorse every one of his views and repudiate all the views of his opponents is pure illusion. The issues are so many and the permutations and combinations of possible

attitudes toward these issues are so great, that the people's selection on election day cannot possibly reflect their diversity of opinion, let alone provide any sort of mandate to whomever may be elected. Furthermore, it is distressing but true that in these times a vote may quite often be *against* something rather than *for* anything or anybody.

The recent national election brought all this to the fore. There was no clear mandate for either of the major presidential candidates nor was there a clear expression of voter opinion on any important national or even state issue. The voters made few major changes in the Congress or in the state legislature. Yet there was more evidence of public dissatisfaction and even unhappiness about state and national affairs than at any time in recent years.

If indeed it is an illusion that in the American political system the voter decides all the issues on election day by an "I'm for you" or "I'm against you" decision every few years at the ballot box, how then does the American public actually influence government? It cannot be denied that somehow our elected public officials are indeed responsive to their constituents and in most cases to their own consciences as well. They know they must be thus or their constituents are quite likely to vote them out at the next election.

We suggest that the responsible elected official responds to what he believes to be public opinion as well as to what he believes to be right. In fact there is evidence that this is true. An increasing number of elected officials are beginning systematically to poll their constituents for guidance on important issues and also to take pains to explain why they acted as they did when they let their conscience be their guide. It would appear therefore that public opinion should be recognized as the strong, even the determining force by which the American people make known their will. Intangible as it may be, public opinion therefore becomes the most potent force in arriving at governmental decisions. It should be a primary concern for those who would influence or guide these decisions.

There are lessons here for the medical profession and for organized medicine. It is important to help elect capable public officials who are men and women of good conscience and who will be responsive to public opinion no matter what their political party. It is also important that, once elected, these officials be kept intelligently informed

in matters pertaining to health and health care. The medical profession should do all in its power to accomplish both these objectives. But it must be recognized that if these elected officials are of the caliber they should be, they will not be unduly beholden to anyone, no matter who may have helped to elect them, or who may seek to lobby, persuade or educate them, but rather they will respond to their own conscience and to their own understanding of public opinion in their own constituency and elsewhere.

It is suggested that organized medicine now become far more concerned than it has ever been with public opinion. It is the force which has shaped the present and will shape the future of medicine in this state and throughout this nation. It is the primary force which determines the legislative, judicial and executive activities of government at all levels, and it is the primary force which determines the success or failure of free enterprise in this nation whether in the public or private sector of society. Medicine, and particularly organized medicine, should be under no illusions. In fact, it should get on the ball.

Surgical Operation for Heart Failure

HEART FAILURE REPRESENTS inadequacy of blood delivery compared to need. It is usually caused by rather obvious hemodynamic abnormalities of the heart as a pump, such as valve deformities or contractile insufficiency. Manifestations include certain compensatory adaptive phenomena, such as tachycardia, increased blood volume and body water through sodium retention, increased neurohormonal stimulation of the heart, and reduction of muscular energy expenditure. Finally, heart failure terminates in some poorly understood vicious cycles, an obvious example of which occurs when excessive sodium and water retention, after initially increasing cardiac output by augmenting ventricular filling, finally leads to pulmonary edema, hypoxia, acidosis, decreased cardiac per-

formance, and which may in turn aggravate the heart failure.

Non-surgical therapy of heart failure may be considered to have three facets—namely: (1) direct improvement in the mechanical behavior of the heart through such drugs as digitalis and isoproterenol; (2) correction of certain remediable complicating features like arrhythmia, anemia, thyrotoxicosis, rheumatic inflammation and the toxic effects of systemic or endocarditic infection; and (3) finally, interference with adaptive processes when they themselves give rise to symptoms, as occurs when pulmonary congestion results in dyspnea.

Evidence that diuresis directly benefits ventricular mechanics is lacking, and reduced ventricular filling pressure decreases cardiac output. After relieving arterial hypoxia and the work of breathing associated with pulmonary edema, further diuresis may, in fact, depress cardiac output and contribute to circulatory insufficiency.

Modern medicine is armed, then, with two potent tools, each of which is double-edged. On the one hand we have a new battery of potent diuretics to diminish the symptoms of pulmonary edema. But the reverse edge is over-diuresis, which can contribute to the low output state with reduced blood volumes, reduced ventricular filling pressure, hemoconcentration, depleted electrolytes and water intoxication.

The other potent tool is surgical operation on the heart, described elsewhere in this issue by Doctors Stinson and Shumway. They document excellent palliation of the circulatory inadequacy in three-fourths of their patients, selected on the basis of their rapid downhill course to a moribund state. Their results, using standard anesthesiologic, surgical and supportive methods available from any first class cardiac surgical team, demonstrate the efficacy of this approach in properly selected patients. But certainly operation was made more hazardous by the precarious late stage of failure in these patients.

The modern physician inherits an augmented responsibility with the potent new tools available to him. While he can dramatically relieve dyspneic symptoms of pulmonary congestion, he must constantly be alert for an early trend indicating the start of a downhill course. He may contribute to this course by over-diuresis, and also, by delaying, jeopardize the opportunity to achieve a surgical benefit with low risk.

Progress in Reproductive Endocrinology

THE PRESSING PROBLEMS created by rapid population growth have stimulated increasing scientific attention to the understanding of human reproduction. Many aspects of the problem have come under study but in no area has the effort been more rewarding scientifically, or useful in the quest for effective means of family planning, than in reproductive endocrinology.

Progress has been slow and erratic. Periodically rapid progress has been stimulated by new discoveries such as the identification of adenosine monophosphate (cyclicamp) as an intermediary in hormone action and by the observation of chromosomal swelling in association with hormone action, suggesting an effect of hormones on the genetic apparatus of the cell. More often, however, progress has been spurred by the development of new assay techniques for measuring hormones. Such methods permit examination of the plethora of hypotheses engendered by the sparsity of reliable information. In this way, development of the immunoassay has had a profound influence on recent developments in endocrinology, particularly as they relate to the function of glands secreting proteins and polypeptides.

The application of radioimmunoassay procedures to the measurement of gonadotropins in recent years has renewed interest in pituitary gonadotropic function and provided tools which have contributed to our understanding of the human ovarian cycle.

Doctors Swerdloff and Odell have reviewed the current state of knowledge of the biochemistry and physiology of the gonadotropic hormones in this issue of *CALIFORNIA MEDICINE*. They have emphasized recent developments in the radioimmunoassay of luteinizing hormone and follicle stimulating hormone and the application of these assays in man, an area in which they have made key contributions. Their careful consideration and synthesis of available information and extensive bibliography

will serve to keep us abreast of developments in this field.

They have brought to attention some of the methodologic problems which have not been solved. The critical importance of selecting an appropriate reference standard is illustrated by the wide divergence in results obtained by comparison of bioassay and immunoassay of a sample when different reference materials are used. The difficulties in obtaining specific antibodies to LH, FSH and human chorionic gonadotropin (HCG) are mentioned by the authors of the review. Preliminary work in other laboratories suggests that differences in the physical properties of these hormones can be used to separate them before immunoassay. Such techniques provide the needed specificity but increase the technical difficulty of the assay. The finding that FSH is present in almost all subjects studied including very young children and cannot be completely suppressed, is puzzling and raises the question of the presence of non-specific immunoactive material in human plasma, although alternative explanations are provided by the authors.

The bioassay procedures currently used in most clinical laboratories measure total urinary gonadotropins. The problems of making adequate measurements at low gonadotropin levels with these assays are reviewed in some detail. The data in Table 4 of the review illustrates the unreliability of this assay and confirms the clinical experience that moderately elevated urinary gonadotropin levels do not usually indicate primary ovarian failure nor does the failure to find detectable levels prove that the pituitary is not secreting gonadotropin. The use of more specific immunoassay procedures along with the administration of human menopausal gonadotropin to stimulate the ovary and of clomiphene citrate to stimulate the pituitary will provide much more reliable means of assessing gonadal function.

As noted by the authors, immunoassay procedures for human prolactin are not available. The existence of an independent human pituitary prolactin has not been universally accepted because it has not been possible to separate completely prolactin activity from growth hormone activity of human pituitary extracts. (Partial separation can be achieved.) Persuasive circumstantial evidence has accumulated in support of the existence of a separate prolactin. Physiological lactation in puerperal women and inappropriate lactation in amenorrheic patients is not associated with in-

creased plasma immunoreactive growth hormone levels, whereas pigeon crop sac stimulating activity is increased. The metabolic changes associated with increased growth hormone activity are absent. Women with genetic dwarfism, which appears to be due to an isolated growth hormone deficiency, are able to produce milk and to breast-feed their offspring.

Improved methods for gonadotropin assay have already provided useful information concerning the pituitary release and peripheral metabolism of these glycoproteins. Much more must be done to clarify these processes and to further our understanding of such basic processes as the onset of puberty, the control of ovulation, the role of gonadal and gonadotropic hormones in behavior and the influence of the environment on gonadal function. It is hoped that this information will also promote more effective clinical use of the gonadotropins for such purposes as the stimulation of ovulation.

Mycosis Fungoides

MYCOSIS FUNGOIDES REMAINS an enigma not only for the dermatologist, who sees most of the patients, but for the hematologist, pathologist and radiologist who observe these patients in one aspect or another of this disease. A firm diagnosis in the early stages of the disease often is elusive, as with all lymphomas. The course and evolution of so-called "premycotic eruptions," such as parapsoriasis en plaque and poikiloderma atrophicum vasculare, into the malignant tumorous stage cannot be predicted. The cause of mycosis fungoides is completely unknown. If it represents a variety of lymphoma, as many contend, it would have to be classified as Stage IV disseminated type, with a poor prognosis even in the early stages,¹ but this certainly is not true clinically, for many patients survive for years with well-advanced cutaneous disease. On the other hand, many Europeans believe but without much conviction that mycosis fungoides is a variety of malignant reticulosis.

Local x-irradiation has been used in traditional treatment for the tumorous stage. The lesions are

usually radiosensitive and may respond to very low doses (100 to 200 r). In recent years, electron beam has been used for widespread and far-advanced disease.² Due to the low penetration of electrons from the beam this method provides whole body surface irradiation without systemic toxicity. Fortunately, these large and expensive instruments are strategically placed throughout the United States so that nearly all patients requiring such treatment can obtain it when necessary.

Chemotherapy, as used for other malignant diseases, is becoming more widespread. The various agents and combinations are outlined in an excellent summary of the therapy of mycosis fungoides by Haynes and Van Scott.³ They recommend a therapeutic program of gradually escalating intensity which is adjusted to fit the individual patient. Topical nitrogen mustard (HN₂) is considered the "single-most valuable therapy" for the early stages of the disease. Elsewhere in this issue of CALIFORNIA MEDICINE, Arundell and Chan strongly support this view and indicate that dilute solutions of topical nitrogen mustard can also be used to control recurrences of mycosis fungoides following electron beam therapy. In the present account, no instances of contact sensitization to nitrogen mustard were encountered, but most dermatologists who use this therapy have encountered acute allergic contact sensitivity in patients treated with repeated applications.⁴

Topical corticosteroids with occlusion also may cause regression of early lesions and usually decreases erythema and pruritus. As the disease advances the therapeutic program escalates to include local x-irradiation, electron beam and finally systemic chemotherapy in various combinations. Often systemic corticosteroids are recommended.³ Clearly, no major breakthrough has been achieved in treating mycosis fungoides, but a number of therapeutic means are now available that alone or in combination reduce the morbidity of the disease and may improve the prognosis.

REFERENCES

1. Kaplan, H. S.: Clinical evaluation and radiotherapeutic management of Hodgkin's disease and the malignant lymphomas, *New Engl. J. Med.*, 278:892-899, 18 Apr. 1968.
2. Fromer, J. L., Johnston, D. O., Salzman, F. A., Trump, J. G., and Wright, K. A.: Management of lymphoma cutis with low megavolt electron beam therapy: Nine-year follow-up in 200 cases, *So. Med. J.*, 54:769-776, 1961.
3. Haynes, H. A., and Van Scott, E. J.: Therapy of mycosis fungoides, *Prog. Derm.*, 3:1-4, Mar. 1968.
4. Waldorf, D. S., Haynes, H. A., and Van Scott, E. J.: Cutaneous hypersensitivity and desensitization to mechlorethamine in patients with mycosis fungoides lymphoma, *Ann. Int. Med.*, 67:282-290, 1967.

LETTERS *to the Editor*

Responsibility of Medical Schools

To the Editor: We have read with interest the opinions of leaders in the medical community in your forum on the scope and responsibility of medicine. As student leaders who are recent but thoroughly concerned members of that community, we hope our views on medical education and the social responsibility of medical schools can be added to the dialogue initiated by the forum. We believe that medical schools have not dealt adequately with the problems of the physician shortage, curriculum deficiencies, the relationship between teaching and research, and the role of the medical school in its community.

1. *The Physician Shortage.* In his 1961 best-seller *The Status Seekers*, Vance Packard wryly attributed the limited number of physicians produced in the United States to the successful birth control practiced by and for the medical profession. More serious recognition of the health hazards in the growing doctor shortage had been spurred years before by implications of the post-World War II population explosion, the rising level of affluence, and the 1958 Forand Bill. Thus the Bane Committee in its 1959 report to the Public Health Service demanded an "immediate and strenuous program by the nation as a whole to meet the country's essential needs for physicians." That the Bane Committee mandate for more physicians was better heard than heeded by medical educators is the unfortunate background of the present medical manpower shortage. It is scarcely fair to put the onus on the federal government, programmed as it has been by the powerful medical profession to let medicine run its own show.

This is not to repine over past failures of the medical schools, but to emphasize our concern that the schools meet their social responsibility for the medical needs of tomorrow.

2. *Curriculum Deficiencies.* The grand design of the first two years of the medical curriculum has changed little since Flexner wrote in 1925, "shoulder to shoulder, phalanx-fashion, the classes [are] clamped together and kept apart by term and annual examinations to which the students must all alike submit at the appointed time." Flexner spoke for us when he called this "alien to the spirit of scientific or modern medicine or to university life," and we question if it fosters the independence and innovation needed to cope with the medical crisis in the country.

Increasing communication between the classes in medical school has made the students aware of the components of the clinical training before their years on the wards; they share concern over such training with their older cohorts. Though clinical years have recently been improved by elective choices, our training sadly lacks an integrated approach; a lack easier for us to accept in learning basic sciences than in learning how to heal the whole human being. An integrated approach including basic sciences, preventive medicine, diagnosis, therapeutics, and physical medicine is sorely needed.

Behavioral science is often slighted in the overall approach to patient care by many medical school instructors. As Dr. Oliver Cope noted in a recent talk at Harvard Medical School: "There is something more than mere infatuation with hard science which prevents the clinician from being interested in the emotional aspect of the patient. It is a more active neglect, a willful neglect." Dr. Cope also states, "Surveys have shown that students enter medical school with an open mind on behavioral aspects of medicine. Something happens to them in the course of four years. They begin their

internship with a disparaging view of the emotional troubles of their patients."

Costs of treatment are mentioned as though irrelevant to medical care. The instructor whose concern is solely with the technology of care forgets to tell us that at some point care becomes so expensive that patients might rather remain ill than accept a life-long debt for their treatment.

We can sum up our feelings about the curriculum with a sentence from Dr. Leon Eisenberg's graduation address to the 1968 Johns Hopkins medical graduates, "A cynic might be tempted to characterize medical education as the process of providing largely incorrect answers to students who have not asked any questions — incorrect answers, if not when given, then so by the time of practice because of the rate at which new knowledge is obtained—not responsive to questions because the student has not generated his own out of clinical responsibility."

3. *Research and Teaching.* We are curious why the religion of the medical research complex is not to be questioned in a community of scholars, least of all by students. Yet, University of Rochester Dean, Kenneth Clark, wrote in an editorial in *Science*: "It is clearly within the capability of the university to assume an expanded role in dealing with society's problems while assuring that the modes of attack are in accord with scholarly values. If our students, by their protests and dissents, stir us to speed this process, we shall be in their debt."

The mythology which the religious faith in research inspires is particularly striking to us in teaching. If a teacher is a first-rate researcher but cannot or will not *teach*, we are assured that either we must be mistaken (since a leading investigator is naturally a good teacher), or else his teaching does not matter because *he* is learning so much. On the other hand, a sensitive and sentient physician who is an ideal preceptor of the science and art of medicine is pressured to do research, although he may tell us he has no interest in adding to the paper explosion and thinks his colleagues might benefit from his example.

4. *The Medical School and the Community.* To quote Eisenberg again, "The physician must take the initiative in developing health care programs for indigent populations, programs that coordinate social with medical efforts, programs designed to combat dependency and to promote reintegration of the disadvantaged into the mainstream of our

society. All of this will have to be reflected in patterns of medical education that are closely related to the new conditions of practice." But Eisenberg seems to write off the medical schools as source of this "initiative," and to look to them only to "reflect" the new conditions of practice in their patterns of medical education.

We do not write off our medical schools. We believe in the intelligence of our teachers. If only they can be convinced of the need for change, their solutions to the questions we ask may be better than our own.

ERIC WILLIAMS, *President*
Med IV, UCLA

JAY CALDWELL, *President*
Med III, UCLA

DON A. ROGERS, *President*
Med II, UCLA

MARK JANSSEN, *Editor*
PLEXUS 1966-1967

KEVIN MURPHY, *Editor*
PLEXUS 1967-1968

EVAN BELLIN, *Editor*
PLEXUS 1968-1969

ROBERT BUKER, *Chairman*
Student Health Organization, UCLA

Acute Renal Failure Due To a Bismuth Preparation

To the Editor: I am writing to demur at "Acute Renal Failure Due to a Bismuth Preparation" reported by John A. James in the October 1968 issue of CALIFORNIA MEDICINE (pages 317-319). I hold no brief for bismuth sodium triglycollamate (Bistrimate®) which the patient took. I agree that this could well be left to lapse into innocuous desuetude, where I considered it to be. Still, the case report of a patient having renal shut down subsequent to this innocuous drug, and therefore *surely* because of it, is neither good logic nor good pharmacology. A classic example of this post hoc, ergo propter hoc line of reasoning in pharmacologic evaluation was the elderly gaffer who told his son, "That there saltpeter that they fed us during World War I to control our passions—it's beginning to work on me now!"

Before going all out on his indictment of Bistri-mate, Dr. James should weigh more heavily the fact that this patient also had, as he says, "at the same time" penicillin. Painful as it may be to think that a "good guy" like penicillin could also be a Child Molester, it is and has been. It has indeed produced (reported) cases of renal shut down, much more clear-cut in their cause and effect relationship than this case. I would also consider suspicious the fact that this girl had had some fairly severe systemic illness for five days prior to either Bistri-mate or penicillin. Almost any urologist will enthusiastically concur in the fact that people do develop renal shut downs for this reason, or for no discernible reason.

In the Los Angeles area, Dr. James could either run this through MEDLARS data retrieval computer at UCLA, or use the cheaper and more efficient older model data retrieval device, produced by unskilled labor and with no repair, maintenance or amortization cost known as the George X. Trimble. I think that a quick run-through on either of these marvels would suggest to him that his prosecution of Bistri-mate in this case would wind up in a Scotch verdict: "Not Proved."

MURRAY C. ZIMMERMAN, M.D.
Whittier

EDITOR'S NOTE: Dr. Zimmerman's letter was forwarded to the author of the case report in question. His reply is printed in the adjoining column.

The Author Replies

Evidence linking specific toxicity to a specific drug can seldom be proof-positive in the individual case. The exposure cannot be repeated in order to confirm the association, and the possibility of exposure to other toxic agents, known and unknown, can rarely be absolutely excluded.

Renal injury occasionally occurs as a manifestation of hypersensitivity to penicillin, although acute renal failure is exceptionally rare. Many of these patients have rashes, fever or other evidence of hypersensitivity. A renal biopsy would have been helpful in excluding this possibility. Bismuth sodium triglycollamate, however, is not as "innocuous" as Dr. Zimmerman implies; this drug was implicated in two of the recent cases of acute bismuth nephrotoxicity cited in the case report. The clinical manifestations and laboratory findings were entirely consistent with acute bismuth intoxication in our patient, and of course the usage of bismuth is infinitesimal compared with that of penicillin.

The weight of circumstantial evidence implicating bismuth in this case seems to me overwhelming. However, I will concede the point to Dr. Zimmerman that the man caught speeding in the stolen car may not always be the thief.

JOHN A. JAMES, M.D.
Los Angeles

IDENTIFICATION OF "MYXEDEMA MADNESS"

"Some patients with myxedema may present with so-called 'myxedema madness' or appear to have what may be a psychosis. If one is not thinking of the possibility of myxedema in such patients, they may be misdiagnosed as schizophrenic or psychotic and treated as such without having proper therapy instituted. These patients have completely reversible psychoses with substitution of thyroid therapy."

—BERTRAM J. CHANNICK, M.D., Philadelphia
Extracted from *Audio-Digest General Practice*, Vol. 16, No. 29, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

California Medical Association



Skin Testing for Allergy— The Role of the Registered Nurse

A Joint Statement by the California Medical Association, the California Nurses' Association and the California Hospital Association

THE ABOVE ASSOCIATIONS are parties to this statement and acknowledge their acceptance of the right of registered nurses to perform allergy skin testing, but only if all the following conditions exist:

1. If the nurse has had competent teaching in the techniques, and
2. The nurse performs the techniques upon the order of a licensed doctor of medicine, and
3. The order relates to a specific patient, and
4. A licensed doctor of medicine is within the vicinity of the clinic where the skin testing is being administered and can immediately and without delay attend the patient at the clinic upon the request of the registered nurse in the clinic.
5. When a hospital has determined that a registered nurse may administer skin tests, the procedure be performed within the framework of designated preparation and practice of the nurse established for the hospital or agency by the committee composed of representatives from the Medical Staff, the Department of Nursing and the Administration; this framework of preparation and practice to be reproduced in writing and made available to the total Medical and Nursing Staff.

Emphasis is placed upon the need for competent and adequate teaching in the techniques; such proper training should come from physicians thoroughly familiar with the techniques, their limitations and their related problems.

June 15, 1968.

Proposed CMA Constitutional Amendment

FOR ACTION IN 1969

One Constitutional amendment was introduced in the 1968 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. The language in parenthesis is to be deleted. In addition, the proposed Constitutional amendment is required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

1 1 1

CHARTERS, ARTICLE I, SECTION 5

Constitutional Amendment 1-68
Introduced by: The Council

Committee 4

Resolved: That Article I, Section 5 of the Constitution of this Association be amended by deleting the language in parentheses, so that the section will now read:

Section 5.—Component Society Charters

Charters to component societies may be granted and revoked as hereinafter prescribed. (, subject to the limitation that only one charter may be outstanding at any one time in any county.)

(Notwithstanding the foregoing,) One charter may be issued to a component society that is not limited as to geographical area or which overlaps the area covered by one or more existing component societies.

❧ In Memoriam ❧

ALBAUGH, CLARENCE J., Los Angeles. Died 9 May 1968 of carcinoma of the lung, aged 89. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1908. Licensed in California in 1942. Doctor Albaugh was a member of the Los Angeles County Medical Association.



BIGLER, ALEXANDER BOWMAN, Chowchilla. Died 14 September 1968 in Chowchilla, aged 64. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Doctor Bigler was a member of the Merced-Mariposa Medical Society.



CROSSLAND, PAUL MARION, Santa Rosa. Died 30 September 1968 in Santa Rosa of cerebral vascular accident, aged 64. Graduate of the University of Minnesota Medical School, Minneapolis, 1931. Licensed in California in 1950. Doctor Crossland was a member of the Sonoma County Medical Society.



DAVID, RUFUS A., Los Angeles. Died 11 October 1968 in Los Angeles of bronchopneumonia, aged 82. Graduate of Chicago College of Medicine and Surgery, Illinois, 1914. Licensed in California in 1921. Doctor David was a member of the Los Angeles County Medical Association.



DORSCH, WILLIAM A., Sun City, Arizona. Died 20 October 1968 in Arcadia, California, of cancer, aged 73. Graduate of Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1922. Licensed in California in 1936. Doctor Dorsch was a retired member of the Los Angeles County Medical Association and

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

the California Medical Association, and an associate member of the American Medical Association.



GLENN, THOMAS HAIGH, Los Angeles. Died 9 October 1968 in Los Angeles of arteriosclerosis, aged 89. Graduate of Northwestern University Medical School, Chicago, Illinois, 1913. Licensed in California in 1917. Doctor Glenn was a member of the Los Angeles County Medical Association, a life member of the California Medical Association and a member of the American Medical Association.



LEVITIN, JOSEPH, San Francisco. Died 12 October 1968 in San Francisco of heart disease, aged 67. Graduate of University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Doctor Levitin was a member of the San Francisco Medical Society.



MOORE, LEE C., Pasadena. Died 18 October 1968 in Pasadena, aged 52. Graduate of Des Moines Still College of Osteopathy, Des Moines, Iowa, 1952. Licensed in California in 1955. M.D. degree from California College of Medicine, 1962. Doctor Moore was a member of the Los Angeles County Medical Association.



NELSON, FRED H., SR., Los Angeles. Died 11 October 1968 in Los Angeles of cerebral vascular accident, aged 80. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, Los Angeles, 1912. Licensed in California in 1912. Doctor Nelson was a member of the Los Angeles County Medical Association.



NICHOLS, WALTER E., Pasadena. Died 24 September 1968 in La Jolla of cerebral vascular accident, aged 93. Graduate of New York Medical College, Flower and Fifth Avenue Hospitals, New York City, 1903. Licensed in California in 1903. Doctor Nichols was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



PRICE, JOSEPH L., Redding. Died 17 September 1968 in Redding of heart disease, aged 57. Graduate of State University of Iowa College of Medicine, Iowa City, 1937. Licensed in California in 1943. Doctor Price was a member of the Shasta-Trinity County Medical Society.

PRUETT, WILLIAM CLIFFORD, Oakland. Died 23 July 1968 in Encino of cerebral vascular accident, aged 87. Graduate of College of Physicians and Surgeons of San Francisco, 1904. Licensed in California in 1904. Doctor Pruett was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



PUTNAM, HARRISON A., Los Angeles. Died 27 October 1968 in Los Angeles of generalized arteriosclerosis, aged 91. Graduate of College of Medicine of the University of Southern California, Los Angeles, 1904. Licensed in California in 1904. Doctor Putnam was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



RATHBONE, ROBERT H., Los Angeles. Died 24 October 1968 in Los Angeles, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Doctor Rathbone was a member of the Los Angeles County Medical Association.



SHAFFER, LEROY EUGENE, Richmond. Died 1 October 1968 in Berkeley of hypertensive cardiovascular disease with coronary atherosclerosis, aged 42. Graduate of University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1954. Doctor Shaffer was a member of the Alameda-Contra Costa Medical Association.

SIZER, EDGAR R., Laguna Beach. Died 4 October 1968, aged 61. Graduate of Northwestern University Medical School, Chicago, Illinois, 1937. Licensed in California in 1938. Doctor Sizer was a member of the Orange County Medical Association.



STEWART, WENDY, Northridge. Died 18 September 1968 in Los Angeles, aged 62. Licentiate of the Royal College of Physicians of London, 1930. Licensed in California in 1930. Doctor Stewart was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



SWANSON, FREDERICK, Los Angeles. Died 29 September 1968 in Beverly Hills of heart disease, aged 50. Graduate of Chicago Medical School, Illinois, 1945. Licensed in California in 1955. Doctor Swanson was a member of the Los Angeles County Medical Association.



WESSELS, WALTER FREDERICK, Los Angeles. Died 22 June 1968 of cardiovascular renal disease, aged 88. Graduate of University of Illinois College of Medicine, Chicago, 1903. Licensed in California in 1911. Doctor Wesseles was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.



ZALL, MORTON, Beverly Hills. Died 24 October 1968 of heart disease, aged 55. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1936. Licensed in California in 1940. Doctor Zall was a member of the Los Angeles County Medical Association.

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GAYLORD HOTEL 3355 Wilshire Boulevard	\$14-16	\$18-22	\$45-70

SEND TO: California Medical Association Housing Bureau
Ambassador Hotel, 3400 Wilshire Boulevard, Los Angeles 90005

Please reserve the following accommodations for the CMA's 1969 Annual Session in Los Angeles, March 15-19.

Single Bedroom \$..... Twin-Bedded \$..... Double Bed \$..... Suite \$.....

First Choice Hotel..... Second Third.....

Arrival (date)..... Hour.....^{a.m.}_{p.m.} Departure (date)..... Hour.....^{a.m.}_{p.m.}

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: Officer?..... Delegate?..... Alternate?..... Speaker?.....

Address: County

City and State..... Zip Code.....

GUESTS' NAMES AND ADDRESSES:

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	California Medical Association For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 240.
LLU:	Loma Linda University For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	Pacific Medical Center For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	Stanford University For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304. (415) 321-1200, ext. 5940.
UCD:	University of California, Davis For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0335.
UCI:	University of California — California College of Medicine, Irvine For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5221.
UCLA:	University of California, Los Angeles For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6756.
UCSD:	University of California, San Diego For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	University of California, San Francisco For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	University of Southern California For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

JANUARY

January 4-18—**Arrhythmia Recognition and Management for Anesthesiologists.** Daniel Freeman Hospital, Los Angeles. Three Saturdays. Contact: Walter Graf, M.D., Chairman, Cardiology Section, Daniel Freeman Hospital, 3701 Stocker Street, Los Angeles 90008.

January 4-February 2—**Medicine Around the World, Highlighting Project Hope in Ceylon.** PMC in Honolulu, Hong Kong, Manila, Bangkok, Singapore, Colombo, Bombay, New Delhi, Agra, London. \$200.

January 7-June 10—**Medical Radio Conferences.** UCSF. Tuesdays, 12:30-1:30 p.m.

January 8-March 12 — **Group Methods.** UCSF at VA Hospital, San Francisco. Wednesdays.

January 9-10—**New and Old Antibiotics.** USC at CD Auditorium, LAC-USC Medical Center. Thursday-Friday. \$35.

January 11—**Cardiac Arrhythmias—A Review of Complex Arrhythmias.** PMC. Saturday. \$50.

January 11-12—**A Conference in Psychiatry.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

January 12—**Use and Abuse of Antibiotics.** Hollywood Community Hospital, Los Angeles. Sunday, 9:30-4:30. \$10. Contact: Marianne Tanenhaus, Staff Secretary, Hollywood Community Hospital, 5245 DeLongpre Avenue, Hollywood 90028. (213) 462-2271.

January 13-March 31—**Psychiatric Principles in Medical Practice.** USC Postgraduate Psychiatry Division at Santa Barbara Cottage Hospital. Mondays, 7-9 p.m. 24 Hours. Contact: Ronald Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, ext. 336.

January 13-17—**An Intensive Course in Otolologic Surgery.** Los Angeles. Monday-Friday. \$300. Contact: Los Angeles Foundation of Otolology, 2130 West Third Street, Los Angeles 90057.

January 14-15 — **Recent Advances in Cardiovascular Therapy.** Sacramento Medical Center. Tuesday-Wednesday. \$35. Contact: Dean T. Mason, M.D., Section of Cardiology, University of California, Davis, School of Medicine, Davis 95616. (916) 752-2930.

January 15—**Midwinter Symposium on Heart Disease.** Statler Hilton Hotel, Los Angeles. Wednesday. Contact: Los Angeles County Heart Association, 2405 West 8th Street, Los Angeles 90057. (213) 385-4231.

January 15-April 2—**Psychiatric Principles in Medical Practice.** USC Postgraduate Psychiatry Division at Upland-Ontario. Wednesdays. \$35. Contact: Ronald Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, ext. 336.

January 15-April 2—**Psychiatric Principles in Medical Practice.** USC Postgraduate Psychiatry Division at Riverside General Hospital. Wednesdays. \$35. Contact: Ronald Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, ext. 336.

January 17-18—**Drug Therapy.** UCSF. Friday-Saturday.

January 18—**Gynecological Endocrinology.** PMC. Saturday.

January 20-24—**Midwinter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 West Olive Avenue, Burbank.

January 21-23—**Society of Thoracic Surgeons.** Hilton Inn, San Diego. Tuesday-Thursday. Contact: Francis X. Bryon, M.D., Executive Secretary, Society of Thoracic Surgeons, City of Hope Medical Center, 1500 East Duarte Road, Duarte 91010.

January 21-April 8—**Psychiatric Patient Management for the Medical Practitioner.** USC Postgraduate Psychiatry Division at Arizona State Hospital, Phoenix. Thursdays, 7-9 p.m. \$35. Contact: Ronald Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, ext. 336.

January 23-25—**Adolescent Medicine.** USC at Frontier Hotel, Las Vegas. Thursday-Saturday.

January 24-June 13—**Nuclear Medicine.** USC at LAC-USC Medical Center. Fridays.

January 24-April 29—**Clinical Psychiatry for Non-Psychiatrists:** A Course in Medical Psychotherapy. UCSF. Fridays.

January 24-26 — **Pediatric Anesthesiology.** Children's Hospital of Los Angeles. Friday-Sunday. Contact: Wayne Herbert, M.D., Program Director, Children's Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles 90027. (213) 663-3341.

January 25—**Gout.** PMC. Saturday.

January 25—**West Coast Postgraduate Course.** CMA, San Luis Obispo Medical Society and USC in San Luis Obispo. \$10.

January 25-26—**Annual Scientific Seminar.** Memorial Hospital of Southern California, Culver City. Saturday-Sunday. Contact: David M. Brotman, M.D., Medical Director, Memorial Hospital of Southern California, 3828 Hughes Avenue, Culver City. (213) 839-4311.

January 26-29 — **Surgical Anatomy.** LLU. Sunday-Wednesday. 32 hours. \$150.

January 29-February 1—**Western Society for Clinical Research.** Village Theatre, Carmel. Wednesday-Saturday. Contact: James E. Bryan, Executive Secretary, American Federation for Clinical Research, 2000 P Street, N.W., Washington, D.C. 20036.

January 30-31—**SOUTHERN COUNTIES—Regional Postgraduate Institute** presented by California Medical Association in cooperation with USC and Southern Counties Medical Societies. El Mirador Hotel, Palm Springs. Thursday-Friday. 12 hours. \$20. Contact: CMA.

January 30-February 1—**Adolescent Medicine.** USC at Sahara Hotel, Las Vegas. Thursday-Saturday.

January 31-February 2—**To Live in Space.** UCSF. Friday-Sunday.

January 31-February 2—**Profile of an Athlete.** UCSF. Friday-Sunday.

FEBRUARY

February 1—**Cancer.** PMC. Saturday.

February 1-2—**Pediatric Neurology.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

February 1-2 — **Seminar in Pediatric Urology.** Children's Hospital of Los Angeles. Saturday-Sunday. \$65. Contact: H. H. Edelbrock, M.D., Seminar Director, Children's Hospital of Los Angeles, 6753 Hollywood Boulevard, Suite 706, Los Angeles 90028.

February 1-2—**Midwinter Radiological Conference.** International Hotel, Los Angeles. Saturday-Sunday. 14 hours. \$30. Contact: Cal Williams, M.D., 15107 Van Owen, Van Nuys 91401.

February 1-2—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Saturday-Sunday.

February 2-5—**Surgical Anatomy.** LLU. Sunday-Wednesday.

February 4-April 22—**Bedside Cardiology.** USC. Tuesdays.

February 4-28—**Medical Centers of the South Pacific.** USC in Pago Pago, Sydney, Melbourne, Christchurch, Auckland, Suva, Papeete. 4 weeks. \$225.

February 6-April 24—**Neuroradiology.** USC at LAC-USC Medical Center. Thursdays.

February 6-8—**Pediatric Ophthalmology.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

February 8—**Coronary Artery Disease: Recent Trends in Diagnosis and Treatment.** PMC. Saturday. \$35.

February 8-9—**Financial Tax and Investment Planning.** UCLA. Saturday-Sunday.

February 8-9—**Drugs: Psychedelic and Narcotic.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

February 10-14 — **Course for Physicians in General Practice.** UCSF at Mount Zion Hospital, San Francisco. Monday-Friday.

February 13—**Infections in the Newborn.** Los Angeles. Thursday. Contact: Mrs. Eve Black, Executive Secretary, Los Angeles Pediatric Society, P.O. Box 2022, Inglewood 90305.

February 14-15—**Regional Meeting, Northern California and Nevada American College of Physicians.** San Francisco. Friday-Saturday. Contact: John R. Gamble, M.D., Governor, Northern California and Nevada Region, ACP, 655 Sutter Street, San Francisco 94102.

February 14-16 — **Ophthalmology and Dermatology.** UCSF. Friday-Sunday.

February 15-16—**Pediatric Neurology.** UCLA. Saturday-Sunday.

February 16-20—**LLU Alumni Postgraduate Convention.** Loma Linda Medical Center and Ambassador Hotel, Los Angeles. Sunday-Thursday. \$50 or \$15/3-hour course. Contact: Samuel H. Fritz, M.D., General Chairman, 1832 Michigan, Los Angeles 90033.

February 17-March 12 — **Sacramento Valley Circuit Courses.** California Medical Association in cooperation with UCD and Sacramento Valley Counties Medical Societies. Mt. Shasta, Chico, Auburn. Mondays, Tuesdays, Wednesdays. 12 hours. \$20. Contact: CMA.

February 18-April 22—**Teaching Clinics in Psychiatry.** UCLA. Tuesdays.

February 19-20—**Symposium on Shock.** USC at Statler Hilton Hotel, Los Angeles. Wednesday-Thursday.

February 21-22—**Regional Meeting, Southern California American College of Physicians.** Santa Barbara. Friday-Saturday. Contact: W. Philip Corr, M.D., Governor, Southern California ACP, 1220 Arlington Avenue, Riverside.

February 21-March 7—**Spatial Analysis of EKG and Arrhythmias.** USC in La Paz, Puerto Vallarta, Acapulco and Mazatlan. 2 weeks. \$200.

February 22-23—**Family Counseling.** USC Division of Postgraduate Psychiatry at Arizona State Hospital, Phoenix. Saturday-Sunday. 12 hours. \$25. Contact: Ronald Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, ext. 336.

February 26-28 — **Neuroelectric Conference.** Jack Tar Hotel, San Francisco. Wednesday-Friday. Contact: David V. Reynolds, Ph.D., Stanford Research Institute, 333 Ravenswood Avenue, Building 18, Menlo Park 94025.

February 26-March 2—**Surgery.** UCLA in Palm Springs. Wednesday-Sunday.

February 28-March 1—**Congenital and Hereditary Defects of the Musculo-Skeletal System.** UCSF. Friday-Saturday.

February 28-March 1 — **Therapy in the Ambulatory Pediatric Patient.** Sacramento Inn. Friday-Saturday. Contact: J. Garland Stroup, M.D., Program Chairman, Sacramento Pediatric Society, 2628 El Camino Avenue, Sacramento 95821.

MARCH

March 1—**Application of Casts, Splints, and Bandages.** UCLA. Saturday.

March 1-2—**NIMH Program.** UCSF at Herrick Memorial Hospital, Oakland. Saturday-Sunday.

March 1-2—**Psychiatry for General Practitioners,** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 1-2—**Computers—Horizons in Biology.** UCSF. Saturday-Sunday.

March 2-5—**Controversial Areas in Gastroenterology.** UCLA in Palm Springs. Sunday-Wednesday.

March 4-8—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. \$30/day; \$125, entire course.

March 5-June 11—**Nuclear Medicine.** UCSF. Wednesdays.

March 6-8—**Nuclear Medicine.** UCSF. Thursday-Saturday.

March 7-8 — **Clinical Neurology: Recent Advances.** UCSF. Friday-Saturday.

March 7-12—**American Association of Pathologists and Bacteriologists.** Hilton Hotel, San Francisco. Friday-Wednesday. Contact: J. L. Orbison, Executive Secretary, American Association of Pathologists and Bacteriologists, University of Rochester, Rochester, New York 14620.

March 8-9—**Children's Hospital Program II.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

March 9-11—**Videotape Self Observation.** UCLA in Palm Springs. Sunday-Tuesday.

March 10-21 — **Workshop in Mental Retardation.** UCLA. 10 days.

March 11-15—**Diagnostic Radiology.** UCSF. Tuesday-Saturday.

March 14-15—**Medical Aspects of Well Being—Death and Dying.** UCSF. Friday-Saturday.

March 15-16—**Psychiatric Program.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 15-16—**Techniques of Surgery of the Shoulder.** UCLA. Saturday-Sunday.

March 15-19 — **CALIFORNIA MEDICAL ASSOCIATION—Annual Scientific Assembly.** Ambassador Hotel, Los Angeles. Saturday-Wednesday. Contact: CMA.

March 19—**San Francisco Neurosurgical Society.** Oak Knoll Naval Hospital. Wednesday evening, 6 p.m. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

March 21-23 — **Children with Learning Disorders.** UCSF. Friday-Sunday.

March 21-23—**New Concepts in the Diagnosis and Management of Pump and Electrical Failure of the Heart.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

March 22—**American Society of Clinical Oncology.** Hilton Hotel, San Francisco. Saturday. Contact: Mary E. Sears, M.D., Treasurer, American Society of Clinical Oncology, M. D. Anderson Hospital, Houston, Texas 77025.

March 22-23—**Postgraduate Assembly in Anesthesiology.** Statler Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: David D. Cohen, M.D., Chairman, Postgraduate Assembly, Los Angeles County Society of Anesthesiologists, 18025 Parthenia Street, Northridge.

March 23-25 — **American Association for Cancer Research.** San Francisco. Sunday-Tuesday.

March 24-28 — **The Clinical Evaluation of Children with Learning Disorders.** UCSF. Monday-Friday. \$100.

March 26—**Spring Symposium for Physicians Practicing General Medicine.** Statler Hilton Hotel, Los Angeles. Wednesday. Contact: Los Angeles County Heart Association, 2405 West Eighth Street, Los Angeles 90057. (213) 385-4231.

March 26-27 — **Coronary Care and Rhythm Disturbances.** USC at Statler Hilton Hotel, Los Angeles. Wednesday-Thursday.

March 27-29—**Uveitis.** UCSF. Thursday-Saturday.

March 28—**Physicians' Symposium on Cardiovascular Diseases.** Hacienda Hotel, Fresno. Friday. Contact: Frances J. Cuthbertson, Executive Director, Central Valley Heart Association, 1759 Fulton Street, Fresno.

March 28-29—**Proctology.** UCSF. Friday-Saturday.

March 29—**Athletic Injuries.** UCLA. Saturday.

March 29-30 — **Transcultural Psychiatry — Mexican-Americans.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 31-April 2—**American Association for Thoracic Surgery.** Fairmont Hotel, San Francisco. Monday-Wednesday. Contact: Thomas B. Ferguson, M.D., Executive Secretary, Suite 311, 7730 Carondelet Avenue, St. Louis, Missouri 63110.

WOMAN'S AUXILIARY

to the California Medical Association



Physicians' Benevolence Fund, Inc.

"DESTITUTE DOCTORS: Hundreds Need Help." This was the eye-catching title of an article in *Medical Economics* under date of 30 September 1968. Although the article was primarily about a physicians' aid program that has been supported by the New York Medical Association and its auxiliary since 1919, the cases cited could have been lifted from the California files or those of many other states.

The article spoke of a physician who had been bedridden on and off for years, and whose savings had gone largely into hospital bills. He had had to sell many of his personal effects just to survive, and, "too proud to seek help from friends or welfare agencies, the old gentleman struggled along in abject poverty." The article went on to say that this aged doctor is one of several hundred throughout the United States who, for a number of different reasons, live a marginal economic existence at a time when the country and the medical profession are enjoying their greatest affluence.

Where do such people go for help? Charitable organizations founded by their colleagues seem to provide the most satisfactory solution to their problems. Many state associations now have such doctor-welfare organizations which offer financial

help ranging from small payments to an M.D.'s widow to an allotment for an indigent physician's entire family. The Physicians' Benevolence Fund, Incorporated, of California is one of the most outstanding of these state programs. It was incorporated as a non-profit organization in 1955, and it is unique in that it covers all of the things done in other states and also helps support the Physicians' Home and Elizabeth Manor Sanitarium in Los Angeles. No other state medical association has provided the means for such institutions.

These facilities are available to members of the California Medical Association, their wives, widows and parents. The warmth, friendliness, careful supervision, kindly personal interest, attractive surroundings and good food all add up to what is known as tender loving care. Visitors are immediately impressed by the "climate," and it seems fitting that those who have devoted their lives to caring for others should in turn be so sheltered and cherished. Those who live in the home and sanitarium pay what they are able to pay, and all receive the same care regardless of financial circumstances. Individual arrangements are completely confidential.

Many of the California doctors and their wives do not understand the scope of the Physicians' Benevolence Fund, nor do they understand how close it is to their personal and professional lives. Besides subsidizing the Los Angeles facilities, the Fund provides aid for doctors incapacitated by crippling diseases or injuries, and helps tide their families over difficult periods when they are deprived of their breadwinner. In case of sudden death the Fund helps sustain the widow and minor children until such time as she can find employment. In many instances it has helped a doctor's children to complete their education in order to

become self-supporting and able to assist with family problems. The Fund has aided elderly physicians and their wives when assets dwindled, so that they were able to remain in their own homes or apartments.

The need for such aid is increasing rather than diminishing, and more and more county medical society aid programs are being implemented to augment the state association project. At present, income for Physicians' Benevolence is derived from one dollar a year per member from the California Medical Association, voluntary contributions from the auxiliaries, and interest earned by investments and loans. It is hoped that the auxiliaries will eventually establish a procedure for consistent support at a state level just as the CMA has. Their voluntary contributions are increasing each year

and during the year 1967-68 they contributed a total of \$4,886, which was \$1,000 more than was contributed during any previous year.

Physicians and their wives may help by bringing needy cases to the attention of the Operating Committee for Physicians' Benevolence, by contacting Mr. Lytton O. Hetland, CMA Staff Coordinator, 693 Sutter Street, San Francisco, California 94102; telephone 776-9400, area code 415. Many would be surprised at the number of such cases they might find in their own areas. All requests for aid are kept completely confidential, and persons in need should be encouraged to avail themselves of the help provided by their associates. Physicians Benevolence takes care of our own.

MRS. CLAIRE E. PIKE

Chairman of Physicians' Benevolence

STATING THE PEDIATRIC DIAGNOSIS TO THE MOTHER

"While you're in the examining room, give full and undivided attention to the child you're seeing. Listen to the mother's questions. The child may have the sixteenth case of diarrhea you have seen that day; but for the mother it's her very own child, and she doesn't want flippant answers. Explain in a simple, unalarming fashion what the diagnosis is, and if it's vague explain what you have to do . . . in the way of laboratory or x-ray tests [to arrive at a clearer one]. Be positive; avoid such expressions as 'I think we ought to do a blood count. What do you think?' and 'What do you think about an x-ray?' You don't ask the mother what she thinks. You tell her what you think. Parents come to you for advice; they want to be followers, not leaders. (An exception to this are the avid column readers who basically come to a doctor suspecting him or wanting to dictate the treatment. This type of patient should be warned of the pitfalls of this kind of medicine; and if you lose the debate, get rid of the patient.) This does not mean that you can't say you don't know what the diagnosis is; that's perfectly acceptable. What isn't acceptable is your inability to know in which direction to go in order to pursue the diagnosis."

—MILTON I. ARNOLD, M.D., Los Angeles

Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.

Director, State Department of Public Health

Erythroblastosis Fetalis Can Be Prevented

AN IMMUNE GLOBULIN, Rh₀ (D) Immune Globulin (Human), is now available which prevents erythroblastosis fetalis.¹ Injected in an Rh negative mother within 72 hours after each delivery of an Rh positive infant, or following a spontaneous or therapeutic abortion, the serum gives the mother passive and transient immunity which prevents the development of active immunity against Rh positive red blood cells. Suppression of active antibodies in the mother protects the infant in the subsequent pregnancy against erythroblastosis fetalis.

The serum may save as many as 500 lives a year in California. In 1964, the most recent year for which data are available, erythroblastosis fetalis caused a total of 454 deaths in California, 6 percent of the state's fetal and 2.5 percent of its neonatal deaths, with a three-to-one ratio of fetal to neonatal deaths.

About 13 percent of all women are Rh negative. Ten percent of these Rh negative women are sensitized in each pregnancy. Based on estimates of women at risk among primigravidas, multiparas and those undergoing miscarriages and therapeutic abortions, the number of Rh negative women in California who annually require protection with immune globulin is approximately 51,000. Once immunized by Rh positive cells, a woman cannot benefit from the serum.

California's physicians have long been concerned with the reduction of mortality from erythroblastosis fetalis. More than two years ago the California Medical Association's Committee on Maternal and Child Care, in conjunction with the Bureau of Maternal and Child Health of the State Department of Public Health undertook a study of mortality from hemolytic diseases of the newborn

[reported in CALIFORNIA MEDICINE, August 1966,²] in which general practitioners, obstetricians, pediatricians, anesthesiologists, pathologists, hematologists and public health physicians participated.

Now that an immune globulin has been developed to prevent erythroblastosis fetalis, cooperation between physicians, hospitals, health jurisdictions and agencies concerned with the care of women in their child-bearing years is essential. The first step is identification of the women at risk, and for this reason it is now imperative that Rh blood typing be included as part of every prenatal blood examination. The second step is that physicians keep in mind the possible use of immune globulin Rh₀ (D) when prescribing the treatment of Rh negative women with Rh positive infants.

It is significant that the California Hospital Association legal counsel has advised California hospital administrators to obtain an adequate supply of the immune globulin and to document carefully instances of patient refusal to accept the immunization.

It is expected that schools of medicine and public health and programs of continuing and in-service medical education will include prevention of erythroblastosis fetalis as an aspect of present-day medical practice.

Official and voluntary health and medical agencies may wish to direct a statewide information and education program to the lay public through appropriate media. Women should learn the importance of the Rh factor, the circumstances under which they may be sensitized, and how this can be prevented.

Cooperation of physicians, hospitals, laboratories and a well-informed public in a program to prevent erythroblastosis fetalis will make it possible to reduce infant mortality and morbidity, always a goal of California's medical community.

REFERENCES

1. For the prevention of Rh isoimmunization, RhoGam, Rh₀ D Immune Globulin (Human), Ortho Diagnostics, Raritan, New Jersey 08869.
2. Siegel, E., Chinnock, R. F., Hyman, C. B., Kushner, J. H., Bates, T., Lewis, A., Gilbert, A., and Corsa, L., Jr.: Hemolytic disease of the newborn—Review of deaths in California, CALIFORNIA MEDICINE, 105:81-88, Aug. 1966.



The Physician's BOOKSHELF

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

Christopher's **TEXTBOOK OF SURGERY**—Ninth Edition—
Edited by Loyal Davis, M.D., Professor of Surgery, Emeritus, Northwestern University Medical School. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 1493 pages with 1368 illustrations on 720 figures, \$21.00.

This is the ninth edition of a textbook of surgery which has been well accepted now for over 20 years by the majority of medical students in the country. The book is one of multiple authorship, with outstanding academicians in all areas making sound contributions to the broad scope of modern surgery. The book has been kept up-to-date, and areas such as bioengineering, tissue transplantation, artificial organs, monitoring of critically ill patients, and topics of this type are also included in the standard textbook.

The book has the particular virtue that it is broad in scope but concise, practical and readily understandable. It is written in clear style, is direct in statement, but not dull in composition.

There are two or three other standard textbooks of surgery available at the present time. This particular textbook occupies the intermediary range. It is not as short or superficial as the smaller works, and is not excessively detailed or lengthy in its approach to surgical problems. It emphasizes principles rather than technique, and is an excellent textbook of surgery for student and general practitioner. The book covers the areas of general surgery and the major surgical specialties, including thoracic, genitourinary, orthopedic and other surgical specialty problems. It can be strongly recommended to the student as an outstanding textbook of surgery.

VICTOR RICHARDS, M.D.

* * *

CLINICAL RADIATION PATHOLOGY—Volume I and Volume II—
Philip Rubin, M.D., Professor of Therapeutic Radiology and Radioisotopes and Associate in Medicine and Surgery, University of Rochester School of Medicine; and George W. Casarett, Ph.D., Professor of Radiation Biology and Biophysics, University of Rochester School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. Volume I—pp. 1 to 517 (plus Index), and Volume II—pp. 518 to 1057 (plus Index); \$45.00 the set.

A logical and stimulating approach to the clinical problems of radiotherapy is presented in this superbly written monograph by therapeutic radiologist Philip Rubin and pathologist George W. Casarett. In developing a biological basis for radiation therapy, the authors correlate the clinical events and symptoms occurring during and after irradiation with the histopathologic changes in tumor and host tissue systems. The radiotherapist is thereby given guideposts to a more intelligent approach to a plan of therapy and significantly to the prevention and treatment of its complications.

The literature of the past several decades abounds with information on the in vivo effects of radiation in humans and animals, but it is to the authors' credit that the importance of this information for clinical application is brought to full realization. The data seems to be the most pertinent, current, and reliable. Wherever capable of extrapolation to clinical use, knowledge from molecular and in vitro cellular research levels is presented.

The monograph, therefore, is an invaluable reference for the radiotherapist, researcher, and resident radiologist. It surpasses in clinical applicability the usual text on radiobiology and complements rather than replaces the standard works on radiotherapy. It begins with concise but thorough depiction of cellular and tissue radiopathology, essential to the complete appreciation and understanding of the subsequent material. Current concepts of nuclear structure are well defined.

Each of the following 18 chapters outline, with a superbly organized repetitive format, the pattern of events or clinical course to be expected during and after each stage or period of irradiation of a specific tissue system. The symptoms, diagnosis, treatment, and prognosis of each clinical effect is defined from the acute through the late or delayed stages, and is then followed by the cellular and histopathologic findings as well as the radiopathologic basis for the above events. A most valuable inclusion is the effect of irradiation on other tissues and systems physiologically or anatomically related.

The authors constantly stress the dynamic interaction and dependence of all tissues, their supporting stroma, relative radiosensitivity, and their differentiating cell population kinetics. Thereafter, the variable physical and biological factors affecting these responses are presented, i.e., the functions of time, dose, fractionation, or quality of radiation; or the effects of age, sex, circulation, or pre-existing disease. Of surpassing value, the *Therapeutic Implications* at each chapter's end presents a philosophical appraisal of what has been discussed and how it might influence the conduct of a course of radiotherapy.

The last seven chapters give current material on Oxygen and Chemotherapeutic modification of radiation response, on Radiation Carcinogenesis, Radiation Syndromes, Radiation effects on Fetus and Embryo, on Sensitivity and Resistance of Tumors, and lastly on the Radiopathologic basis for the Time-Dose Relationship.

The text is well published with excellent illustrations and well captioned for ready access to the material. It should find a frequented place in the library of the cancer therapist, radiologist or oncologist, the radiology resident, and the radiobiologic researcher.

LLOYD GILLIN, M.D.



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KEY TO ABBREVIATIONS USED

(BRP)—Bureau of Research and Planning; (CMA)—California Medical Association; (CR)—Case Report; (Ed.)—Editorial; (I)—Information; (LE)—Letter to Editor; (MP)—Medical Progress; (MSC)—Medical Staff Conference; (N/N)—News and Notes; (Or.)—Original Article; (PE)—Page End; (PHR)—Public Health Report.

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